Neuronale Korrelate der Belastung durch chronischen Tinnitus

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Hiermit erkläre ich, dass ich diese Dissertation selbständig, ohne unerlaubte Hilfe und ohne Nutzung anderer Quellen als den genannten angefertigt habe.

Göttingen, den 10.01.13 Dennis Golm

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Vorbemerkung zur Grundlage der kumulativen Dissertation

Bei der vorliegenden Arbeit handelt es sich um eine publikationsbasierte Dissertation. Grundlage der Arbeit sind zwei englischsprachige Artikel, die bei internationalen Zeitschriften *(peer-reviewed*) veröffentlicht (1. Aufsatz) bzw. zur Publikation eingereicht (*submitted*) wurden (2. Aufsatz).

Golm, D., Schmidt-Samoa, C., Dechent, P. & Kröner-Herwig, B. (2013). Neural correlates of tinnitus related distress: An fMRI-study. Hearing Research 295, pp. 87- 99.

Golm, D., Schmidt-Samoa, C., Dechent, P. & Kröner-Herwig, B. (submitted). Tinnitus-related distress: Evidence from fMRI of an Emotional Stroop Task.

Beide Studien wurden in Kooperation mit der Forschungsgruppe MR-Forschung in der Neurologie und Psychiatrie der Abteilung Kognitive Neurologie der Georg-August-Universität Göttingen durchgeführt. Bei beiden Arbeiten war ich grundlegend beteiligt, mir oblagen die Entwicklung des experimentellen Designs, die Planung und Durchführung der Studie, die statistische Auswertung und Interpretation der Daten sowie die Ausarbeitung und Veröffentlichung der Manuskripte.

Der vorliegende Rahmentext soll die beiden Artikel inhaltlich zusammenführen. Im ersten Teil der Arbeit erfolgt eine theoretische Einführung in die Thematik und die Ableitung der Fragestellung, gefolgt von einer Zusammenfassung der Methoden, Ergebnisse und Diskussion der Studien. Abschließend werden die Ergebnisse der Artikel in Hinblick auf ihre Bedeutsamkeit für das Forschungsfeld diskutiert. Im zweiten Teil der Arbeit werden die Originalartikel präsentiert.

Inhaltsverzeichnis

Zusammenfassung

Subjektiver Tinnitus bezeichnet eine Geräuschwahrnehmung in Abwesenheit einer objektivierbaren Schallquelle. Etwa 5% der Bevölkerung sind von chronischem Tinnitus betroffen, von denen etwa 17% stark unter dem Ohrgeräusch leiden. Dieses Leiden hängt dabei nur schwach mit der Lautheit des Tinnitus zusammen. Unter anderem werden Aufmerksamkeitsfokus auf den Tinnitus und seine dysfunktionale Bewertung als Bedingungen für die Tinnitusbelastungsentstehung und -aufrechterhaltung gesehen. Verschiedene neurophysiologische Modelle betonen eine Rolle limbischer Regionen bei Tinntusbelastung. Daneben sollen frontale Regionen und der Precuneus eine Rolle spielen, wobei mehrere Studien besonders eine Beteiligung frontaler und limbischer Areale bei Tinnitusbelastung unterstützen.

Ergänzend zu Resting-State Studien sollten neuronale Korrelate von Tinnitusbelastung erstmalig in einem aufgabengeleiteten (task-driven) Ansatz mittels funktioneller Magnetresonanztomographie untersucht werden. In zwei Studien wurden hoch und niedrig belastete Tinnitusbetroffene sowie gesunde Kontrollprobanden untersucht Die Aktivierung von Hirnregionen, die mit Tinnitusbelastung assoziiert sind, sollte in Studie 1 über die Darbietung negativer tinnitusbezogener Sätze angeregt werden. In Studie 2 wurde ein *Emotional Stroop Task* eingesetzt, um Prozesse selektiver Aufmerksamkeit auf tinnitusbezogene Wörter und deren emotionale Verarbeitung zu untersuchen.

In Studie 1 zeigte die hoch belastete Gruppe stärkere Aktivierungen in frontalen und limbischen Arealen gegenüber gesunden Kontrollprobanden, sowie im Vergleich zu niedrig belasteten Tinnitusbetroffenen im linken mittleren frontalen Gyrus. Tinnitusbelastung korrelierte erwartungskonform mit der Stärke der Aktivität limbischer und frontaler Regionen. In Studie 2 zeigte sich auf Verhaltensebene kein Interferenzeffekt für tinnitusbezogene Wörter bei hoch belasteten Probanden. Neuronal zeigten hoch belastete Tinnitusbetroffene stärkere Aktivierungen in der rechten Insula und frontalen Arealen gegenüber der niedrig belasteten Gruppe. Es gab keine hypothesenkonformen Unterschiede im Vergleich zu gesunden Kontrollprobanden. Die Höhe der Tinnitusbelastung korrelierte allerdings erwartungskonform mit der Stärke der Aktivität in der rechten Insula und dem rechten inferioren frontalen Gyrus.

Übereinstimmend fand sich in beiden Studien eine Beteiligung des linken mittleren und des rechten inferioren frontalen Gyrus sowie der zentralen Insula. Der linke mittlere frontale

Gyrus könnte eine Funktion bei der Aufrechterhaltung negativer tinnitusbezogener Information im Arbeitsgedächtnis haben, während der rechte inferiore frontale Gyrus mit der Salienz von Reizen in Verbindung gebracht wird. Der zentrale Teil der Insula ist mit Interozeption assoziiert, die eng mit emotionaler Verarbeitung in Beziehung steht. Der linke mittlere und der rechte inferiore frontale Gyrus könnten sich als Zielregionen für neuromodulatorische Ansätze eignen. Zukünftige Studien sollten hochbelastete Tinnitusbetroffene vor und nach einer belastungsreduzierenden kognitiven Verhaltenstherapie mittels funktioneller Magnetresonanztomographie untersuchen.

I. Synopsis der Publikationen

1. Theoretischer Hintergrund des Forschungsprojektes

1.1 Subjektiver Tinnitus– Definition, Symptome und Epidemiologie

Subjektiver Tinnitus bezeichnet eine Geräuschwahrnehmung in Abwesenheit einer objektivierbaren Schallquelle (Møller, 2011a). Dieses Phantomgeräusch kann ein einzelner Ton unterschiedlicher Frequenz oder auch ein komplexes Geräusch sein (Møller, 2011a). Etwa 5% der Bevölkerung sind von chronischen Ohrgeräuschen betroffen (Fabijanska, Rogowski, Bartnik, Skarzynski, 1999; Palmer et al., 2002). Etwa 17% der chronisch betroffenen leiden stark unter dem Ohrgeräusch (Axelsson & Ringdahl, 1989). So kann es zu Konzentrationsschwierigkeiten, Schlafproblemen, Beeinträchtigung der Stimmung und Hörproblemen kommen (Andersson & Kaldo, 2004). Das Ausmaß der wahrgenommenen Belastung korreliert dabei nur schwach mit psychoakustischen Merkmalen des Tinnitus, wie z.B. seiner Lautheit (Henry & Meikle, 2000).

1.2 Entstehung von Tinnitus

Eines der am weitesten verbreiteten Modelle der Tinnitusentstehung beschreibt das Ohrgeräusch als Folge einer sensorischen Deprivation des auditorischen Systems, die durch Hörverlust entsteht. Gründe für eine verminderte Hörfähigkeit sind vielfältig. Beispielhaft sei eine Haarzellenschädigung aufgrund eines Schalltraumas genannt, ebenso wie Störungen innerhalb des Mittelohrs oder auch eine Blockierung des Ohrkanals. Hörverlust kann über zwei Mechanismen Tinnitus verursachen: die Veränderung des Verhältnisses von Inhibition und Exzitation sowie neuroplastische Veränderungen (Møller, 2011b).

Wenn pathologische Veränderungen innerhalb der Cochlea zu einer stärkeren Reduktion inhibitorischer im Vergleich zu exzitatorischen Prozessen führen, können die Neuronen eines Zellverbandes so stark aktiviert werden, um in Abwesenheit externer auditorischer Reize eine Geräuschwahrnehmung (Tinnitus) zu erzeugen. So konnte gezeigt werden, dass eine selektive Schädigung von Haarzellen in der Cochlea, wodurch das auditorische Summenpotential im Hörnerv reduziert wird, bei etwa 50% der Neuronen im inferioren Colliculus zu einer erhöhten Feuerungsrate führt. Dieses Phänomen ist nach Wang, Ding & Salvi (2002) durch einen Verlust der lateralen Inhibition erklärbar. Es existieren Hinweise darauf, dass Töne im Hochfrequenzbereich stärkere inhibitorische Einflüsse auf Neuronen im cochlearen Nucleus haben als niederfrequente

Töne. Somit könnte die häufig auftretende Hochtonschwerhörigkeit durch eine Reduktion der im Regelfall begleitend auftretenden Inhibitionsprozesse Tinnitus erzeugen (Møller, 2011b).

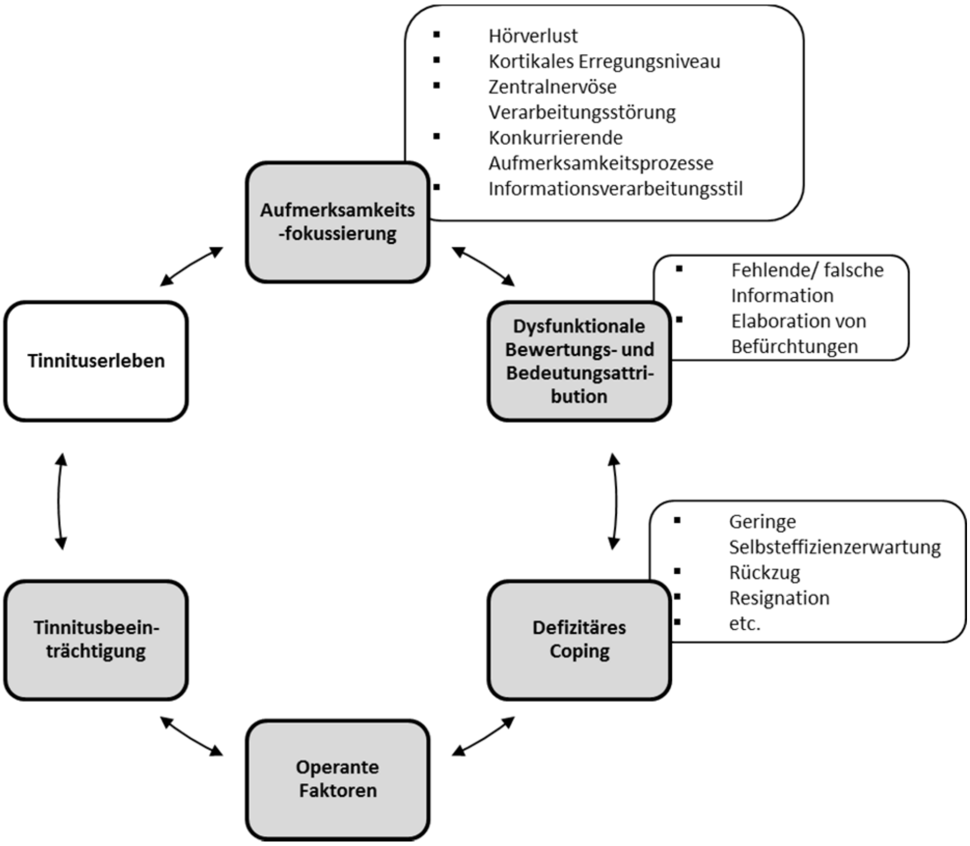
Neuroplastische Veränderungen können ebenfalls Folge einer sensorischen Deprivation des auditorischen Systems sein. So könnten als Folge einer Haarzellenschädigung langfristig tonotopische Veränderungen entstehen, wobei angrenzende Zellen ihren Repräsentationsbereich auf die Zellen ausweiten, welche die Sektionen der Läsion im peripheren Rezeptor repräsentieren. Innerhalb dieser periläsionalen Regionen könnte es dann zu erhöhter Synchronizität kommen, da mehr Zellen dieselbe Funktion übernehmen. Eine mögliche Konsequenz dieser erhöhten Synchronizität könnte Tinnitus sein (Bartels, Staal & Albers, 2007).

1.3 Entstehung und Aufrechterhaltung von Tinnitusbelastung

Die alleinige Wahrnehmung eines Ohrgeräuschs ist allerdings keine hinreichende Bedingung für die Entwicklung einer Anpassungsstörung bei Tinnitusbetroffenen, d.h. der Tinnitusbelastung. Für deren Erklärung schlägt Hallam (1987) ein multifaktorielles Habituationsmodell vor. So sei die *normale* Reaktion auf ein bedeutungsloses auditorisches Signal, was Tinnitus eigentlich ist, die Gewöhnung an das Geräusch. Eine Tinnitusbelastung soll danach erst dann entstehen, wenn sich die Aufmerksamkeit der Betroffenen auf das Ohrgeräusch richtet und es zu Interferenzen mit anderen Aktivitäten kommt, die Aufmerksamkeit benötigen (z.B. ein Gespräch), oder der Tinnitus als Gefahrensignal interpretiert wird (z.B. „Ein Hirntumor verursacht die Ohrgeräusche.“).

Mertin und Kröner-Herwig (1997) sahen neben der fehlenden Habituation ungünstige *Coping-Strategien* (z.B. vermeidendes Coping) und *operante Konditionierungsprozesse* (z.B. negative Verstärkung) als Bedingungen für die Tinnitusbelastungsentstehung und integrieren diese Faktoren in ein Teufelskreismodell (siehe Abbildung 1). Nach diesem Teufelskreismodell fokussieren die Betroffenen ihre Aufmerksamkeit auf das Ohrgeräusch und schreiben dem Tinnitus eine negative Bedeutung zu, wodurch es zu einer Belastungsreaktion kommt, die durch einen Mangel an geeigneten Bewältigungsstrategien sowie operante Prozesse verstärkt bzw. aufrechterhalten wird.

Abbildung 1: Ein Teufelskreismodell des Tinnitus aus Mertin und Kröner-Herwig (1997)



1.3.1 Dysfunktionale Bewertungs- und Bedeutungsattributionen bei Tinnitus

Tatsächlich scheint den im Teufelskreismodell (Mertin & Kröner-Herwig, 1997) genannten dysfunktionalen Bedeutungszuschreibungen eine besondere Rolle zuzukommen. So berichteten hoch belastete Tinnitusbetroffene mehr tinnitusspezifische negative Kognitionen als niedrig belastete Tinnitusbetroffene (Henry & Wilson, 1995), wohingegen es keine Unterschiede zwischen den Gruppen hinsichtlich der Anzahl allgemein negativer Gedanken gab (Henry &Wilson, 1995). Dies konnte in weiteren Studien dieser Art bestätigt werden. So korrelierte die emotionale Belastung durch Tinnitus zu r= .56 mit dysfunktionalen Gedanken über Tinnitus (Lee, Kim, Hong & Lee, 2004). Dabei wurde der Einfluss des *Tinnitusschweregrades* (operationalisiert über Zeit seit Einsetzen des Tinnitus, subjektive Lautstärke und Wahrnehmungsdauer des Tinnitus pro Tag) auf die Tinnitusbelastung durch kognitive Prozesse wie *dysfunktionale Annahmen über Tinnitus* und *katastrophisierende Gedanken* mediiert. Eine moderierende Rolle dysfunktionaler Annahmen auf die Tinnitusbelastung wird durch eine Studie von Henry und Wilson (1998) gestützt, in der kognitive Umstrukturierung als alleinige Intervention, zu einer Reduktion der Tinnitusbelastung im Vergleich zu einer Wartegruppe führte.

1.3.2 Aufmerksamkeitsfokussierung und Tinnitusbelastung

Neben dysfunktionalen Gedanken in Bezug auf Tinnitus spielt der Aufmerksamkeitsfokus auf das Ohrgeräusch eine wichtige Rolle bei der Aufrechterhaltung der Tinnitusbelastung (Mertin & Kröner-Herwig, 1997). So konnte gezeigt werden, dass Tinnitusbetroffene mit unilateralem Tinnitus ihre Aufmerksamkeit eher auf das Ohr richten, das dem Ort der Wahrnehmung des Tinnitus zugeordnet war (Cuny, Norena, Massioui & Chéry-Croze, 2004). In einem auditorischen *Oddball*-Paradigma war die Anzahl korrekter Reaktionen einer Gruppe von Tinnitusbetroffenen mit unilateralem Tinnitus auf einen Zielton höher, wenn dieser auf dem Ohr dargeboten wurde, auf dem sie das Ohrgeräusch „wahrnahmen". Kontrollprobanden, die keinen Tinnitus hatten, aber stattdessen zusätzlich ein tinnitusähnliches Geräusch dargeboten bekamen (hochfrequentes Breitbandrauschen), zeigten diesen Effekt nicht.

Zudem scheint die einfache Fokussierung der Aufmerksamkeit auf das Ohrgeräusch die erlebte Tinnitusbelastung zu verstärken (Rief, Sander, Günther & Nanke, 2004). So schätzte eine Gruppe von Tinnitusbetroffenen ihre Tinnitusbelastung höher während der Lenkung der Aufmerksamkeit auf das Ohrgeräusch, als bei Entspannung ein. Dieser Effekt wurde auch von physiologischen Parametern gestützt, so war die Herzrate höher bei Aufmerksamkeitslenkung auf den Tinnitus als bei Ablenkung. Diese Befunde werden von den Ergebnissen einer schwedischen Studie gestützt (Andersson, Jüris, Classon, Frederikson & Furmark, 2006), in der die Belastung durch Tinnitus höher war während Aufmerksamkeit auf den Tinnitus gerichtet war, im Vergleich zur Ablenkung durch Rechenaufgaben. Es gibt auch den komplementären Befund, wo sich zeigte, dass sich bei intensiver erlebter Tinnitusbelastung der Aufmerksamkeitsfokus auf das Ohrgeräusch verstärkt. In einer Studie zu ereigniskorrelierten Potentialen (EKP) (Delb et al., 2008) wurden den Studienteilnehmer auf dem rechten Ohr bzw. dem Ohr, auf dem sie den Tinnitus „wahrnahmen", Tonimpulse dargeboten. In einem ersten Versuchsteil sollten die Studienteilnehmer per Knopfdruck auf einen Zielton reagieren, im weiteren Verlauf sollten sie den Ton ignorieren. Während die niedrig belasteten Tinnitusbetroffenen von der ersten (Aufmerksamkeit auf Zielton) zur zweiten Bedingung eine Reduktion in zwei EKP-Maßen der Aufmerksamkeit zeigten, war dies bei den hoch belasteten Tinnitusbetroffenen nicht zu beobachten. Es fällt hoch belasteten Tinnitusbetroffenen also schwer Aufmerksamkeit vom Tinnitus abzuziehen.

Andersson und Westin (2008) sahen in der Aufmerksamkeit auf Tinnitus einen Mediator zwischen Tinnituswahrnehmung und -belastung, nämlich dann wenn der Tinnitus negativ bewertet wird. Cima, Crombez und Vlaeyen (2011) fanden eine positive Korrelation zwischen dem Ausmaß katastrophisierender Bewertungen und der Stärke des Aufmerksamkeitsfokus auf Tinnitus. Die Fokussierung der Aufmerksamkeit auf den Tinnitus und die negative Bewertung des Ohrgeräuschs scheinen also zwei miteinander assoziierte, aufrechterhaltende Prozesse der Tinnitusbelastung zu sein.

1.4 Neuronale Korrelate von Tinnitusbelastung

Gemäß dem *Neurophysiologischen Modell* von Jastreboff, Gray & Gold (1996) entsteht Tinnitusbelastung durch eine initial negative Bewertung des Ohrgeräuschs (z.B: „Ich werde taub“). Ein subcortikales neuronales Signal wird auf kortikaler Ebene als Tinnitus wahrgenommen und als bedrohlich bewertet, wodurch es zu einer negativen emotionalen Reaktion bei Aktivierung des limbischen Systems kommt. Dies soll einerseits das Tinnitussignal selbst verstärken und zum anderen das autonome Nervensystem aktivieren, wodurch es zu einer Stressreaktion kommt. Auch in diesem Modell führt eine negative Bewertung des Ohrgeräuschs zu Tinnitusbelastung, so dass limbische Hirnareale bei hoch belasteten Tinnitusbetroffenen stärker aktiviert sein sollten, als bei wenig belasteten.

Kürzlich erfuhr dieses Modell durch die Annahmen von Schlee, Lorenz, Hartmann, Müller & Schulz (2011) im sogenannten *Global Brain Model* eine Erweiterung. Dies postuliert bei chronischem Tinnitus einen modulierenden Einfluss eines fronto-parietal-cingulären Netzwerks auf die Aktivität im auditorischen Kortex (siehe 1.2). Der Top-Down-Einfluss soll dabei durch das Ausmaß der Tinnitusbelastung mediiert werden: je höher die Belastung durch den Tinnitus, desto stärker ist der Top-Down-Effekt und desto höher ist die Aktivität im auditorischen Kortex. Kernstrukturen sollen dabei der dorsolateral präfrontale Kortex, der orbitofrontale Kortex, das anteriore Cingulum sowie der Precuneus und der posteriore cinguläre Kortex sein.

In jüngster Zeit wurde von De Ridder, Elgoyhen, Romo & Langguth (2011a) ein noch differenzierteres Modell als das *Global Brain Model* postuliert, das Tinnitus als ein Phänomen mehrerer, sich überlappender Netzwerke begreift. Neben einer Beteiligung des auditorischen Kortex sowie von Gedächtnisarealen, geht das Modell von einem sogenannten *Wahrnehmungsnetzwerk*, einem *Salienz*- und einem *Belastungsnetzwerk* aus. Zusätzlich zu einer Aktivierung des auditorischen Kortex ist danach eine Aktivierung des Wahrnehmungs- und des Salienznetzwerkes für die bewusste Wahrnehmung eines Phantomgeräuschs notwendig. Gedächtnisareale sollen eine Rolle bei der Persistenz der Bewusstheit des Tinnitus und der Verstärkung der Tinnitusbelastung spielen (siehe Tabelle 1). Somit lässt sich dieses Modell als das beste Abbild des von Mertin und Kröner-Herwig (1997) beschriebenen Teufelskreismodells auf neuronaler Erklärungsebene verstehen, da es neben der reinen Tinnituswahrnehmung kognitiv-emotionale Verarbeitungsprozesse differenziert berücksichtigt.

Tabelle 1: Multiple parallele überlappende Subnetzwerke des Phänomens Tinnitus (nach De Ridder et al., 2011a)

Neuronale Areale	**FC**	**PC**	**Prec**	**sACC**	**dACC**	**PCC**	**AI**	**Amyg**	**Parahip**	**Hipp**
Prozessebenen										
Wahrnehmung	x	x	x	x	x	x				
Salienz					x		x			
Belastung				x	x		x	x		
Gedächtnis								x	x	x

AI= anteriore Insula, Amyg= Amygdala, dACC= dorsaler anteriorer cingulärer Kortex, FC= frontaler Kortex, Hipp= Hippocampus, Parahip= Parahippocampus, PC= parietaler Kortex, PCC= posteriorer cingulärer Kortex, Prec= Precuneus, sACC= subgenualer anteriorer cingulärer Kortex

Ein Überblicksartikel derselben Arbeitsgruppe (Vanneste & De Ridder, 2012) schließt auch eine Rolle präfrontaler Areale bei der emotionalen Verarbeitung des Ohrgeräuschs nicht aus. So ist nach diesen Autoren der dorsolateral präfrontale Kortex mit Tinnitusbelastung und auditorischer Verarbeitung assoziiert. Der orbitofrontale Kortex spielt danach zusammen mit der Insula eine Rolle in der Top-Down-Modulation autonomer Reaktionen auf emotionale Erfahrungen. Jastreboff (1990) hatte schon früher eine Funktion des präfrontalen Kortex in der Integration sensorischer und emotionaler Aspekte des Tinnitus vermutet.

Die meisten Befunde zu neuronalen Korrelaten der Tinnitusbelastung stammen aus Resting-State Studien mit der Ausnahme der Studie von Schlee, Weisz, Bertrand, Hartmann und Elbert (2008). Hier wurde die funktionale Konnektivität verschiedener Hirnregionen bei Tinnitusbetroffenen und gesunden Kontrollprobanden während des Hörens verschiedener Töne erfasst.

Die Tinnitusbetroffenen hörten entweder einen Ton, welcher der Frequenz ihres eigenen Tinnitus entsprach (Tinnituston-Bedingung) oder Kontrolltöne anderer Frequenz. Bei den Kontrollprobanden wurde der sogenannte *Tinnituston* aus einem ähnlichen Frequenzspektrum wie bei der Tinnitusgruppe zufällig ausgewählt. Eine erhöhte funktionelle Konnektivität zwischen Aktivität im rechten Frontallappen und dem anterioren cingulären Kortex sowie zwischen dem rechten Parietalllappen und dem anterioren cingulären Kortex korrelierte mit der Penetranz des Ohrgeräuschs (Subskala des Tinnitusfragebogens von Goebel und Hiller (1998)). Eine detaillierte Auflistung bisheriger Befunde zu neuronalen Korrelaten der Tinnitusbelastung findet sich in Tabelle 2.

Die Mehrzahl der Studien unterstützt die Beteiligung frontaler und limbischer Strukturen an der Tinnitusbelastung. Es zeichnet sich allerdings kein völlig einheitliches Bild ab, was zumindest zum Teil an den unterschiedlichen bildgebenden Verfahren und ihrer räumlichen Auflösung bzw. dem Auflösungsniveau, auf dem Befunde berichtet werden, liegen kann. Legt man eine grobe Definition über Brodmann Areale (BA) für den dorsolateralen präfrontalen Kortex (BA 9, 46) und den orbitofrontalen Kortex an (BA 10, 11, 47 inklusive inferiorer frontaler Gyrus), dann finden sich Belege für eine Beteiligung sowohl des orbitofrontalen (De Ridder et al., 2011b, Burton et al., 2012), als auch des dorsolateralen präfrontalen Kortex (De Ridder et al., 2011b, Vanneste et al., 2010). Die besondere Rolle des präfrontalen Kortex für die Tinnitusbelastung wird auch durch Studien zum Einsatz neuromodulatorischer Verfahren bei Tinnitus gestützt. So erreichte eine Gruppe von Tinnituspatienten drei Monate nach 10 Stimulationssitzungen mit repetitiver transkranieller Magnetstimulation (rTMS) bei einer kombinierten Stimulation des temporalen und präfrontalen Kortex eine größere Reduktion in der Tinnitusbelastung als eine Gruppe, die ausschließlich temporale Stimulation erhalten hatte (Kleinjung, et al., 2008). Ebenso konnte mittels transkranieller Gleichstrom-Stimulation (tDCS) am dorsolateralen präfrontalen Kortex eine Reduktion in Tinnituslautheit und –belastung erzielt werden (De Ridder & Vanneste, 2012). Von den limbischen Regionen spielen vermutlich sowohl das anteriore und posteriore Cingulum, der parahippocampale Gyrus als auch die Insula eine Rolle bei Tinnitusbelastung. Die Rolle des Precuneus ist weniger gut belegt. So finden Schlee et al. (2009) eine Korrelation zwischen der Stärke des Einflusses anderer Hirnregionen (strength of inflow) auf die Aktivität im temporalen Kortex und der Höhe der Tinnitusbelastung. Eine Quelle dieses Einflusses war der Precuneus. Dagegen hat die Aktivität des Precuneus nach Vanneste et al. (2010) keine Vorhersagekraft für die Tinnitusbelastung.

Tabelle 1: Aktivierungen frontaler, limbischer und parietaler Strukturen in bisherigen Studien zu Tinnitusbelastung. Die Genauigkeit der Angaben entspricht denen der jeweiligen Studie.

Verfahren	Studie	Stichprobe	Analyse	Frontal (BA)	Limbisch	Parietal
EEG	De Ridder et al., 2011b	LDT (TF I, II) : n=30 HDT (TF III, IV): n= 25	HDT > LDT	inferiorer FG (47) medialer FG (11, 25) mittlerer FG (11)	ACC Insula parahip. G	
			Korrelation mit TF	inferiorer FG (47) medialer FG (32, 9, 10, 11)	ACC parahip. G	
	Van der Loo et al., 2011*	HLDT (TF): n= 10	Korrelation mit TF		Insula ant R/L	
	Vanneste et al., 2010	LDT (TF I, II): n= 13 HDT (TF III, IV): n=14	HDT > LDT		ACC Amygdala parahip. G	
			LDT > HDT		PCC	Precuneus
			HDT (IV) > (III)		ACC Insula parahip. G Amygdala	
			HDT (III) > (IV)		PCC	Precuneus
			LDT (I) > HDT (III)	DLPFC (9, 46) präzentraler G (6) VLPFC (8)		
			HDT (III) > LDT (I)			Precuneus
			Regression AV: TF UV: ROI	DLPFC	ACC parahip. G PCC	

Fortsetzung Tabelle 1

Verfahren	Studie	Stichprobe	Analyse	Frontal (BA)	Limbisch	Parietal
EEG	Joos et al., 2012	HLDT (TF): n =56	Korrelation mit TF	frontopolarer K R/L OFC (10, 11) R/L Parahip.	ACC sg	
			Korrelation mit TF, Kontrolle für BDI Scores	frontopolarer K R OFC R	ACC	
fMRT	Burton et al., 2012	HDT (THI III, IV): n= 17 HC: n= 17	HDT > HC KA, SR: Insula ant R	inferior FG L		
MEG	Schlee et al., 2009	HLDT (TF I, II, IV): n= 23 HC: n=24	Korrelation mit TF	präfrontaler Kortex	PCC	Precuneus
	Weisz et al., 2005	HLDT (TF I-IV): n=17 HC: n=16	Korrelation mit TF	posteriorer FK L		PK ant L/R
	Schlee et al., 2008	HLDT (TF): n=12 HC= 10	Korrelation funktioneller Konnektivität mit TF	FK R	ACC	PK R

(I, II, III, IV) bezeichnen die jeweiligen Belastungsgrade bezogen auf den verwendeten Fragebogen, ACC= anteriorer zingulärer Kortex, ant= anterior, AV= abhängige Variable, EEG= Elektroenzephalographie, FG= frontaler Gyrus, fMRT= Funktionelle Magnetresonanztomographie, HDT= hoch belastete Tinnitusbetroffene (high distressed tinnitus patients), HLDT= gemischt hoch und niedrig belastete Stichprobe; K= Kortex, KA= Konnektivitätsanalyse, L= links, LDT= niedrig belastete Tinnitusbetroffene (low distressed tinnitus patients), MEG= Magnetenzephalographie, Parahip.= Parahippocampus; Parahip. G= Parahippocampaler Gyrus, PCC= posteriorer zingulärer Kortex, PK= parietaler Kortex, R= rechts, ROI= region of interest, sg= subgenual, SR= seed region, TF= Tinnitusfragebogen, TF I= Tinnitusfragebogen Subskala Penetranz des Tinnitus, THI= Tinnitus Handicap Inventory, UV= unabhängige Variable, * Diese Studie hat ausschließlich die anteriore Insula als ROI untersucht.

1.5 Ziele des Forschungsprojektes

Um die Befunde aus Resting-State Untersuchungen zu ergänzen, wurden erstmalig neuronale Korrelate der Belastung durch Tinnitus in einem aufgabengeleiteten (*task-driven*) Design mittels funktioneller Magnetresonanztomographie (fMRT) untersucht. Dabei wurden hoch und niedrig belastete Tinnitusbetroffene sowie gesunde Kontrollprobanden miteinander verglichen. In keiner der in Tabelle 2 aufgeführten Studien wurde explizit für Schwerhörigkeit als möglicher konfundierender Variable (Melcher, Sigalovsky, Guinan & Levin, 2000) kontrolliert. Dies sollte in der eigenen Untersuchung daher umgesetzt werden.

Die Aktivierung von Hirnregionen, die mit Tinnitusbelastung assoziiert sind, wurde in zwei Studien über unterschiedliche Prozesse angeregt. In Studie 1 wurden den Probanden negative tinnitusbezogene Sätze dargeboten, welche typische dysfunktionale Kognitionen von Tinnitusbetroffenen abbilden sollten. Das Lesen dieser Sätze sollte bei hoch belasteten Tinnitusbetroffenen zu einer Aktivierung eigener ungünstiger tinnitusbezogener Verarbeitungsprozesse führen. Gemäß des Teufelskreismodells (Mertin & Kröner-Herwig, 1997) sollte dies die akut erlebte Tinnitusbelastung erhöhen und damit relevante frontale und limbische Areale sowie gegebenenfalls den Precuneus aktivieren (vergleiche 1.4). In Studie 2 wurde ein *Emotional Stroop Task* eingesetzt, um in Anlehnung an das Teufelskreismodell (Mertin & Kröner-Herwig, 1997) eine selektive Aufmerksamkeit auf tinnitusbezogene Informationen zu untersuchen. Es wurde angenommen, dass tinnitusbezogene Wörter besonders für hoch belastete Tinnitusbetroffene emotional saliente Reize darstellen. Dadurch sollte Aufmerksamkeit von der Aufgabenbearbeitung, die Druckfarbe des Wortes benennen, abgezogen werden und es zu längeren Reaktionszeiten auf diese Wörter im Vergleich zu neutralen Wörtern kommen (Cisler et al., 2011). Die emotionale Verarbeitung dieser Wörter sollte die akute Tinnitusbelastung erhöhen und mit Tinnitusbelastung assoziierte Hirnareale aktivieren, wie sie in den Modellen von Schlee et al. (2010) und de Ridder et al. (2011) angenommen werden. Diese Areale sollten bei hoch belasteten Tinnitusbetroffenen dann stärker aktiviert sein als bei niedrig belasteten Tinnitusbetroffenen und gesunden Kontrollprobanden (siehe unten).

2. Zusammenfassende Darstellung der Studien

In beiden Studien wurden drei Gruppen von alters- und geschlechtsgematchten Probanden untersucht: hoch und niedrig belastete Probanden mit chronischem Tinnitus sowie gesunde Kontrollprobanden ohne Tinnitus. Beiden Studien lagen im Wesentlichen die gleichen Stichproben zugrunde. Die Erfassung des Belastungsgrads und damit die Bildung der Tinnitusgruppen erfolgte über den Tinnitusfragebogen von Goebel und Hiller (1998), dem in Deutschland gebräuchlichsten Instrument zu Erfassung der Beeinträchtigung. Gemäß der im Fragebogen vorgegebenen Skalierung wurden ab Stufe 2 (≥ 31, mittelgradige Belastung) bis Stufe 4 (sehr schwere Belastung) die Probanden der sogenannten hoch belasteten Gruppe zugeteilt, die übrigen der niedrig belasteten Gruppe. Die wichtigsten Kriterien für den Studienausschluss waren eine nicht-deutsche Muttersprache, Vorliegen eines depressiven Syndroms, Hyperakusis (Geräuschüberempfindlichkeit), Schwerhörigkeit, und in Studie 2 Farbenblindheit. Das Vorliegen von Kontraindikationen für eine Untersuchung mittels fMRT wurde selbstverständlich sorgfältig überprüft und führte dementsprechend zur Nichtaufnahme in die Studie. In die letztendliche Stichprobe gingen pro Gruppe 16, mehrheitlich männliche Probanden ein (N= 48). Die hoch belasteten Tinnitusbetroffenen wiesen gegenüber den beiden anderen Gruppen höhere Werte in Skalen der Ängstlichkeit, Depressivität und Geräuschempfindlichkeit auf. Gegenüber der niedrig belasteten Gruppe wiesen sie zusätzlich geringere Werte auf einer Skala zum Wortschatz auf.

Vor der fMRT-Untersuchung nahmen die Probanden zunächst an einem Vortraining teil, um sich mit den unterschiedlichen Aufgaben innerhalb der beiden Studienteile vertraut zu machen. Im Magnetresonanztomographen durchliefen die Probanden insgesamt drei experimentelle Paradigmen: Lesen von visuell dargebotenen Sätzen und Beurteilung ihrer persönlichen Relevanz (Studie 1), Durchführung des *Emotional Stroop Tasks* (Studienteil 2) sowie eines Maskierungsexperiments, welches nicht Bestandteil der vorliegenden Arbeiten ist. Nach der Durchführung der Aufgaben bewerteten die Studienteilnehmer die Stimuli aus Studie 1 (Sätze) und 2 (Wörter) hinsichtlich ihrer Valenz und des *Arousals* auf einer computerisierten Version (Barke, Stahl & Kröner-Herwig, 2011) des Self-Assessment-Mannequin (SAM; Bradley & Lang, 1994) Weitere Details der Studiendurchführung sind den beiden vorgelegten Arbeiten zu entnehmen.

2.1 Emotionale Verarbeitung tinnitusbezogener Sätze (Studie 1)

In Studie 1 sollten über die Darbietung von Sätzen verschiedener Kategorien unterschiedliche kognitiv-emotionale Verarbeitungsprozesse angeregt werden, deren neuronale Repräsentation durch das fMRT erfasst wurde. Dabei wurde davon ausgegangen, dass sich diese abhängig vom Ausmaß der habituellen Tinnitusbelastung der vom Tinnitus betroffenen Probanden unterscheiden sollte. Dazu wurde ein sogenanntes. *Emotionales Satzparadigma* entwickelt, welches Sätze aus drei unterschiedlichen Kategorien präsentierte (pro Kategorie 15 Sätze; Kategorie 1: Selbstaussagen negativen Inhalts (z.B. „Ich werde das Ohrgeräusch niemals los“), Kategorie 2: allgemeine Selbstaussagen negativen Inhalts (z.B. „Ich habe häufig Mitleid mit mir“) und emotional neutrale Selbstaussagen (z.B. „Ich schaue regelmäßig auf meine Uhr“).

Die Darbietung neutraler und allgemein negativer Sätze diente zur Herstellung der Kontrollbedingungen. Zwischen den Kategorien waren die Sätze hinsichtlich Anzahl der Wörter gematcht. Die Sätze wurden randomisiert für 8 Sekunden dargeboten, gefolgt von einem Fixationskreuz für 10, 12 oder 14 Sekunden. Aufgabe der Probanden war es per Knopfdruck der rechten Hand die persönliche Relevanz der Sätze zu beurteilen. Sie sollten auf einem Tasten-Pad die Taste drücken, die der persönlichen Relevanz der Selbstaussage entsprach (Taste 1: niedrige/ keine Relevanz, Taste 2: etwas Relevanz, Taste 3: hohe Relevanz). Als abhängige Variable diente die BOLD- (Blood Level Oxygen Dependent) Antwort der Probanden auf die dargebotenen Sätze. In der Auswertung wurden die neuronalen Aktivierungen infolge der tinnitusbezogenen Sätze mit denen neutraler und allgemein negativer Sätze kontrastiert. Auf Verhaltensebene dienten Ratings der persönlichen Relevanz der Sätze, der Valenz und des Arousals als abhängige Variablen. Vergleiche in der neuronalen Aktivierung und den anderen abhängigen Variablen wurden innerhalb und zwischen den Gruppen berechnet. Zwei weitere Analysen wurden innerhalb der Tinnitus-Gesamtgruppe durchgeführt: eine Korrelationsanalyse der BOLD-Antworten mit der intervallskalierten Tinnitusbelastung sowie eine Konnektivitätsanalyse.

Folgende Hypothesen wurden überprüft:

1. Hoch belastete Tinnitusbetroffene bewerten tinnitusbezogene Sätze als persönlich relevanter, negativer und aufregender als neutrale und allgemein negative Sätze.

2. Im Vergleich zu niedrig belasteten Tinnitusbetroffenen und gesunden Kontrollprobanden bewerten sie tinnitusbezogene Sätze als negativer, aufregender und persönlich relevanter.
3. Neuronal zeigt die hoch belastete Gruppe stärkere Aktivierungen im Precuneus sowie frontalen und limbischen Strukturen in Reaktion auf tinnitusbezogene Sätze im Vergleich zu den Sätzen der beiden anderen Kategorien.
4. Diese Aktivierungen sind stärker im Vergleich zu niedrig belasteten Tinnitusbetroffenen und gesunden Kontrollprobanden.
5. Außerdem korrelieren diese Aktivierungen mit der tinnitusbezogenen Belastung (Gesamtscore des Tinnitusfragebogens).

Im Folgenden werden die wesentlichen Befunde dargestellt, wobei zunächst auf die subjektiven Ratingdaten eingegangen wird. Anders als erwartet gab es bei den Valenz- und Arousalratings keine Unterschiede zwischen den Gruppen. Alle Probanden beurteilten tinnitusbezogene Sätze und allgemein negative Sätze als negativer und aufregender im Vergleich zu neutralen Sätzen. Die persönliche Relevanz tinnitusbezogener Sätze wurde wie erwartet von hoch belasteten Tinnituspatienten höher eingeschätzt als die Relevanz allgemein negativer Sätze. Zudem beurteilten sie die Relevanz tinnitusbezogener Sätze höher als die gesunde Kontrollgruppe und es gab einen Trend (p= .0106) für höhere Relevanzratings tinnitusbezogener Sätze im Vergleich zu niedrig belasteten Tinnituspatienten. Hypothese 1 konnte somit größtenteils bestätigt werden. Hypothese 2 wurde nur zum Teil bestätigt, da sich Unterschiede zwischen den Gruppen nur hinsichtlich persönlicher Relevanz fanden. Es scheint daher, dass der differenzierende Faktor zwischen den Gruppen die höhere Relevanz ist, die hoch belastete Tinnitusbetroffene tinnitusbezogenen negativen Selbstaussagen zuweisen.

Die Hauptresultate der fMRT-Auswertungen werden im Folgenden dargestellt. Bei den hoch belasteten Tinnitusbetroffenen zeigten sich in Übereinstimmung mit den Erwartungen höhere Aktivierungen in Reaktion auf tinnitusbezogene Sätze im Vergleich zu den beiden anderen Satzkategorien in verschiedenen frontalen Arealen sowie dem dorsalen posterioren Cingulum (limbisch) und dem Precuneus. Somit konnte Hypothese 3 bestätigt werden. Im Vergleich zu der Kontrollgruppe zeigten hoch belastete Tinnitusbetroffene erwartungskonform höhere Aktivierungen auf tinnitusbezogene Sätze als auf neutrale Sätze in verschiedenen frontalen (mittlerer, superiorer, medialer frontaler Gyrus, linker inferiorer frontaler Gyrus) und limbischen Arealen (anteriorer cingulärer/ midcingulärer Kortex, Insula, posteriorer cingulärer Kortex, linker parahippocampaler Gyrus), entgegen den Erwartungen allerdings nicht im Precuneus. Sie zeigten ebenso höhere Aktivierungen gegenüber der Kontrollgruppe im Vergleich tinnitusbezogener mit allgemein negativen Sätzen in einem frontalen Areal, dem linken superioren frontalen Gyrus. Widererwartend zeigten sich aber keine Unterschiede in limbischen Regionen und dem Precuneus. Gegenüber niedrig belasteten Tinnituspatienten zeigten sie ausschließlich eine höhere Aktivierung im linken mittleren frontalen Gyrus im Vergleich tinnitusbezogener mit neutralen Sätzen. Hypothese 4 wird somit zum Teil bestätigt.

Hypothese 5 konnte weitgehend bestätigt werden. Innerhalb der Tinnitusgruppe korrelierte Tinnitusbelastung mit der BOLD-Antwort in verschiedenen limbischen (anteriorer midcingulärer Kortex, linker anterior cingulärer Kortex, linke Insula), frontalen (mittlerer, superiorer, medialer frontaler Gyrus, rechter inferiorer frontaler Gyrus) sowie parietalen Strukturen (inferiorer Parietallappen, rechter superiorer Parietallappen). Es wurde allerdings keine Korrelation mit der BOLD-Antwort im Precuneus gefunden.

Da die Aktivität des linken mittleren frontalen Gyrus hoch von niedrig belasteten Tinnitusbetroffenen differenzierte wurde explorativ die funktionelle Konnektivität dieser Region mit anderen Regionen innerhalb der Tinnitusgruppe untersucht. Hoch belastete zeigten gegenüber niedrig belasteten Tinnitusbetroffenen eine höhere funktionelle Konnektivität des linken mittleren frontalen Gyrus mit limbischen (rechter PCC, linke Insula), frontalen (rechter medialer frontaler Gyrus, linker präzentraler Gyrus) und parietalen Strukturen (linker postzentraler Gyrus) Strukturen.

Die Befunde lassen die folgenden Schlussfolgerungen zu. Sie stützen die Beteiligung frontaler Areale, insbesondere des linken mittleren frontalen Gyrus, und limbischer Areale an der emotionalen Verarbeitung von Tinnitus. Der linke mittlere frontale Gyrus wurde mit der Wahrnehmung der Ohrgeräusche in Verbindung gebracht (Weisz, Moratti, Meinzer, Dohrmann & Elbert, 2005; Mirz et al., 1999), wie auch mit der Belastung durch Tinnitus (De Ridder et al., 2011b). Weitere Studien fanden einen Zusammenhang mit der Verarbeitung emotionaler Wörter (Hirata et al., 2007), aufregender Bilder (Dolcos, LaBar & Cabeza, 2004) sowie mit Rumination (Cooney, Joorman, Eugène, Dennis & Gotlib, 2010). Eine Funktion des linken mittleren frontalen

Gyrus bei Tinnitusbelastung könnte daher die Aufrechterhaltung dysfunktionaler Gedanken im Arbeitsgedächtnis sein. Weiterhin weisen die Befunde auf eine Beteiligung des dorsolateralen präfrontalen Kortex bei Tinnitusbelastung hin.

In Übereinstimmung mit anderen Studien unterstützen die Befunde eine Beteiligung der Insula und des posterioren anterioren Cingulums bei Tinnitusbelastung (Vanneste et al., 2010; De Ridder et al., 2011b). Weiterhin wurde aufgrund der Daten unserer Studie erstmalig der anteriore midcinguläre Kortex explizit mit Tinnitusbelastung in Verbindung gebracht. Da der anteriore midcinguläre (Shackman et al., 2011) und der posteriore cinguläre Kortex (Benuzzi, Lui, Duzzi, Nichelli & Porro, 2008) beide mit der Verarbeitung negativer Emotionen in Beziehung gesetzt werden, könnte ihre Aktivität mit der emotionalen Verarbeitung tinnitusbezogener Kognitionen assoziiert sein. Die Insula scheint eine Rolle bei der Regulation des autonomen Nervensystems zu spielen (Nagai, Hoshide & Kario, 2010).

Neben einer Beteiligung frontaler und limbischer Areale betont das *Global Brain Model* (Schlee et al., 2011) die Bedeutung des Precuneus für die Tinnitusbelastung. Diese konnte in der vorliegenden Studie jedoch nicht bestätigt werden. Eine zu geringe Power kann als möglicher Grund für den fehlenden statistischen Nachweis nicht ausgeschlossen werden. Bei einem unkorrigierten p= .02 korreliert die BOLD-Antwort im linken Precuneus mit der Höhe der Tinnitusbelastung, was als Hinweis auf die Richtigkeit dieser Überlegung gesehen werden kann. Insgesamt gesehen scheint es sich um ein unspezifisches Belastungsnetzwerk (De Ridder, 2011) zu handeln, da überlappende Aktivierungen auch bei anderen Phänomenen gefunden wurden, die mit Belastung assoziiert sind: soziale Zurückweisung (Kross, Egner, Ochsner, Hirsch & Downey, 2007), Kurzatmigkeit (von Leupoldt et al., 2009) sowie *medically unexplained symptoms* (Landgrebe et al., 2008).

Eine Schwäche der Studie könnte darin gesehen werden, dass Teilnehmer aus der Gruppe der „hoch belasteten“ in der Mehrzahl, gemessen an der Graduierung des Tinnitusfragebogens, nur einen moderaten Belastungsgrad aufwiesen. Bei einer größeren Unterschiedlichkeit der Gruppen hinsichtlich Tinnitusbelastung hätten sich vielleicht deutlichere Unterschiede in der Aktivierung limbischer Areale gezeigt. Diese Sichtweise wird von den Unterschieden in der Aktivierung der limbischen Areale zwischen hoch belasteten Tinnituspatienten und Kontrollprobanden unterstützt. Es ist jedoch darauf hinzuweisen, dass Tinnitusbetroffene mit einer Belastung, wie sie in unserer Gruppe zu finden war, häufig um Therapie nachsuchen und sich an Behandlungsstudien beteiligen (Kröner-Herwig, Frenzel, Fritsche, Schilkowsky & Esser, 2003; Zachriat & Kröner-Herwig, 2004; Rief, Weise, Kley & Martin, 2005). Auch die Auswahl des Stimulusmaterials (negative tinnitusbezogene Selbstaussagen) könnte in Hinblick auf unsere Untersuchungsabsichten ungünstig gewesen sein. Die Präsentation von für den individuellen Probanden bedeutsamen Kognitionen zum Tinnitus wäre wegen der vermutlich höheren persönlichen Relevanz förderlich hinsichtlich der Untermauerung der Hypothesen gewesen.

2.2 Tinnitusbelastung und selektive Aufmerksamkeit (Studie 2)

Ziel der zweiten Studie war die Identifikation selektiver Aufmerksamkeitsprozesse auf tinnitusbezogene Wörter und die Untersuchung neuronaler Korrelate einer emotionalen Verarbeitung dieser Worte. Zu diesem Zweck wurde der *Emotional Stroop Task* gewählt. Als Wortstimuli wurden tinnitusbezogene Wörter sowie neutrale Kontrollwörter anhand einer Vorstudie ausgewählt und hinsichtlich Wortlänge, Silbenanzahl und Häufigkeit des Vorkommens in der deutschen Sprache gematcht (Meinhardt- Renner & Kröner- Herwig, unveröffentlicht). Um den zusätzlichen Einfluss weiterer Faktoren wie Salienz der Ohrgeräusche (Lautheit des Tinnitus) zu untersuchen, wurde neben den Belastungsscores des Tinnitusfragebogens (Goebel & Hiller, 1998) auch die Tinnituslautheit mit der BOLD-Antwort korreliert. Im Magnetresonanztomographen wurden den Studienteilnehmern Wörter zweier verschiedener Stimuluskategorien blockweise dargeboten: tinnitusbezogene Wörter (z.B. *schrill*) und neutrale Wörter (z.B. *Schrank*). Insgesamt wurden den Teilnehmern 12 Blöcke dargeboten, in denen sie jedes Wort zwei Mal für 1750 ms, gefolgt von einem Fixationskreuz für 250 ms, in einer von vier Farben sahen. Zwischen den Blöcken wurde für 24 Sekunden ein Fixationskreuz gezeigt. Ihre Aufgabe bestand darin per Knopfdruck die Druckfarbe des gezeigten Wortes so schnell wie möglich anzugeben (Taste 1= rot, Taste 2= gelb, Taste 3= blau, Taste 4= grün). Es wurde erwartet, dass hoch belastete Tinnitusbetroffene die Tinnituswörter, im Gegensatz zu den neutralen Wörtern, in emotionaler Weise verarbeiten. Folgende Hypothesen wurden untersucht:

1. Hoch belastete Tinnitusbetroffene beurteilen tinnitusbezogene Wörter als negativer und aufregender im Vergleich zu neutralen Wörtern,
2. Sie beurteilen diese als negativer und aufregender als die niedrig belasteten Tinnitusbetroffenen und gesunde Kontrollprobanden.

3. Hoch belastete Tinnitusbetroffene reagieren langsamer auf tinnitusbezogene Wörter als auf neutrale Wörter.
4. Neuronal zeigen sie höhere Aktivierungen in Reaktion auf tinnitusbezogene im Vergleich zu neutralen Wörtern im Precuneus, in frontalen sowie limbischen Arealen, insbesondere im orbitofrontalen und dorsolateralen präfrontalen Kortex, dem Parahippocampus, dem anterioren und posterioren Cingulum und der Insula.
5. Diese höhere Aktivierung im Kontrast tinnitusbezogener mit neutralen Wörtern sollte sich auch gegenüber niedrig belasteten Tinnitusbetroffenen und gesunden Kontrollprobanden zeigen.
6. Innerhalb der Tinnitusbetroffenen korreliert die BOLD-Antwort im Kontrast tinnitusbezogener mit neutralen Wörtern mit den Tinnitusbelastungswerten in den unter 4. genannten Arealen.

Es zeigten sich die folgenden Befunde. Tinnitusbezogene Wörter wurden generell als aufregender und negativer bewertet. Es ergaben sich widererwartend jedoch keine Unterschiede zwischen den Gruppen. Ebenso wenig zeigten hoch belastete Tinnitusbetroffene Unterschiede in ihren Reaktionszeiten auf neutrale und tinnitusbezogene Wörter. Während Hypothese 1 bestätigt werden kann, müssen Hypothese 2 und 3 abgelehnt werden. Eine mögliche Erklärung für das Fehlen eines Stroop-Effektes könnte sein, dass der visuelle Präsentationsmodus nicht geeignet ist, um Effekte selektiver Aufmerksamkeit bei Tinnitus nachzuweisen. So wären Paradigmen, die auditorische Stimuli benutzen wie z.B. Aufgaben zum dichotischen Hören eventuell besser geeignet. Bei diesen Aufgaben hören Probanden zeitgleich verschiedene Wörter im linken und rechten Ohr, wobei sie neutrale Wörter auf z.B. dem linken Ohr nachsprechen (beschatten) und die Wörter auf dem rechten Ohr ignorieren sollen. Handelt es sich bei den zu ignorierenden Wörtern um emotional saliente Reize, wurden mehr Beschattungsfehler beobachtet (Stetter, 1994; Nielsen & Sarason, 1981).

Neuronal finden sich allerdings Unterschiede innerhalb und zwischen den Gruppen. Innerhalb der hoch belasteten Gruppe zeigte sich eine höhere BOLD-Antwort auf tinnitusbezogene im Vergleich zu neutralen Wörtern in frontalen Arealen (rechter inferiorer frontaler Gyrus, linker superiorer/ mittlerer frontaler Gyrus), der rechten Insula und dem rechten Precuneus. Hypothese 4 wird also bestätigt. In Übereinstimmung mit Hypothese 5 zeigen sich im Vergleich zu niedrig belasteten Tinnitusbetroffenen stärkere Aktivierungen in der rechten Insula, dem rechten inferioren frontalen Gyrus und dem linken mittleren frontalen Gyrus. Es zeigen sich keine Unterschiede im Precuneus. Zwischen hoch belasteten Tinnitusbetroffenen und Kontrollprobanden zeigten sich dagegen keine hypothesenrelevanten Unterschiede. Hypothese 5 kann also nur zum Teil bestätigt werden. Eine zusätzliche Analyse der Unterschiede zwischen den Tinnitusgruppen weist darauf hin, dass niedrig belastete Tinnitusbetroffene im orbitofrontalen Kortex stärker auf die neutralen Wörter reagieren, während hoch belastete Tinnitusbetroffene stärker auf die Tinnituswörter reagieren. Dieses Ergebnis ist konform mit der Annahme, dass niedrig belastete Tinnitusbetroffene ihre Reaktion auf die Tinnituswörter durch Anwendung einer Emotionsregulationsstrategie, wie dem Reappraisal, herunterreguliert haben könnten. So konnten Ochsner et al. (2002). zeigen, dass Reappraisal die Aktivität im orbitofrontalen Kortex senken kann.

In Studie 1 wurden Unterschiede zwischen hoch belasteten Tinnitusbetroffenen zu der gesunden Kontrollgruppe in limbischen und frontalen Arealen gefunden. Die Sätze aus Studie 1 (z.B. „Ich werde das Ohrgeräusch niemals los“) lieferten im Gegensatz zu den Wörtern aus Studie 2 einen klaren Tinnitusbezug. So könnte beispielhaft das Wort *schrill* aus Studie 2 nicht nur mit Tinnitus, sondern auch mit einer schrillen Stimme in Verbindung gebracht werden und somit auch von den Kontrollprobanden als persönlich relevant bewertet worden sein (z.B. Erinnerung an eine schrille Stimme), was das Auffinden von Aktivierungsunterschieden in Reaktion auf diese Wörter erschwert hätte.

Die Stärke der BOLD-Antwort im rechten inferioren frontalen Gyrus und der rechten Insula korrelierte positiv mit der Höhe der Tinnitusbelastung. Es wurden keine Zusammenhänge mit der BOLD-Antwort im Precuneus gefunden. Hypothese 6 kann also weitestgehend bestätigt werden. Es zeigen sich keine Korrelationen mit Tinnituslautheit, Geräuschempfindlichkeit, Ängstlichkeit und Wortschatz. Aktivität der rechten Insula korrelierte zusätzlich auch mit der Höhe der Depressivität. Dies deutet auf eine Aktivierung überlappender neuronaler Netzwerke von Tinnitusbelastung und Depressivität hin, eine Annahme, die schon von Langguth und Landgrebe (2011) aufgestellt wurde und mit der Idee eines unspezifischen Belastungsnetzwerks bei Tinnitus konform geht (De Ridder, 2011). Nach De Ridder et al. (2011a) ist die anteriore Insula, sowohl an der Salienz der Tinnituswahrnehmung, als auch an der Belastung durch diese beteiligt. Laut einer Metaanalyse von Kurth, Zilles, Fox, Laird und Eickhoff (2010) stellt der dorsale Teil der anterioren Insula eine hoch integrative Region verschiedenster Prozesse, wie emotionalkognitiver Verarbeitung und Interozeption dar. Die Insula-Aktivierungen in der vorliegenden Studie liegen im zentralen Teil der Insula, welcher laut Kurth et al. (2010) mit interozeptiver Verarbeitung assoziiert ist, die wiederum in einem engen Zusammenhang zur Wahrnehmung von Emotionen steht (Gray, Harrison, Wiens & Critchley, 2007; Singer, Critchley & Preuschoff, 2009; Critchley, 2005). So schätzten beispielhaft Personen in einem Experiment in dem die Rückmeldung der Herzrate manipuliert wurde, neutrale Gesichter als emotionaler ein, wenn Ihnen zuvor „fälschlich“ ein schnellerer Herzschlag zurückgemeldet wurde. Eine stärkere Aktivität innerhalb der rechten anterioren Insula war assoziiert mit höheren Ratings der Emotionalität bei „falschem“ Herzraten-Feedback (Gray et al., 2007). Das Fehlen einer Korrelation neuronaler Aktivität mit der Tinnituslautheit, welche die Salienz des Ohrgeräuschs widerspiegeln könnte, deutet darauf hin, dass die Aktivität der rechten Insula in der vorliegenden Studie eher die Tinnitusbelastung als die Salienz abgebildet hat. Zusammenfassend kam es anscheinend zu einer emotionalen Verarbeitung der tinnitusbezogenen Wörter. Ihre persönliche Relevanz scheint allerdings nicht stark genug gewesen zu sein, um mit der Aufgabenbearbeitung zu interferieren, wobei gezeigt werden konnte, dass neuronale Prozesse sogar sensitiver sein können als Verhaltenseffekte (Heil & Rolke, 2004; Heil, Rolke & Pecchinenda, 2004). Zukünftige Studien sollten individuelle Tinnituswörter verwenden, um eine hohe persönliche Relevanz der Wörter für die Studienteilnehmer sicher zu stellen.

3. Zusammenfassende Diskussion

3.1 Einschränkungen bei der Interpretation von fMRT-Daten

Die Auswertung von fMRT-Daten ist hoch komplex und bei ihrer Interpretation sind einige Besonderheiten zu beachten. So wird neuronale Aktivität über ein indirektes Maß, den sogenannten BOLD-Kontrast gemessen (Buckner & Logan, 2001). Ob die gemessene Aktivität auf exzitatorische oder inhibitorische Synapsen bzw. eine Kombination aus beiden zurückgeht, ist dabei nicht feststellbar (Buckner & Logan, 2001, Logothetis, 2008). In fMRT- Designs wird oft die Substraktionsmethode verwendet, d.h. die Aktivität in Reaktion auf eine interessierende Bedingung (z.B. Lesen tinnitusbezogener Sätze) wird kontrastiert mit der Aktivität in Reaktion auf eine Kontrollbedingung (z.B. Lesen von Sätzen ohne Tinnitusbezug) (Buckner & Logan, 2001; Shimamura, 2010), es werden demnach *Unterschiede* der neuronalen Aktivität zwischen zwei Aufgaben erfasst. Neben dem interessierenden Prozess (z.B. Verarbeitung tinnitusbezogener Sätze) werden also alle Prozesse, erfasst, in denen sich die Kontrollbedingung zusätzlich von der experimentellen Bedingung unterscheidet (Buckner & Logan, 2001).

Generell handelt es sich um eine korrelative Methode, was bedeutet, dass Aussagen über kausale Zusammenhänge nicht möglich sind (Shimamura, 2010). So stellen Querschnittsstudien mittels fMRT lediglich eine Momentaufnahme neuronaler Prozesse dar, welche sich aus der Interaktion verschiedener Prozesse zusammensetzen kann (Kessler, Traue, Wiswede, 2011): neuronalen Prädispositionen (z.B. für die Entwicklung von Tinnitusbelastung), pathologischen Prozessen (z.B. Veränderungen im Gehirn, die ursächlich für Tinnitusbelastung sind), Veränderungen in Folge einer Symptomatik (z.B. neuroplastische Veränderungen) und kompensatorischen Mechanismen (z.B. aufgrund von Bewältigungsversuchen zum Umgang mit Tinnitus). Um eine bessere Trennung dieser Prozesse zu ermöglichen schlagen Kessler et al. (2011) den Gebrauch längsschnittlicher Designs vor sowie die Kombination verschiedener bildgebender Verfahren bzw. die Verwendung neuer Datenanalysetechniken, wie z.B. Konnektivitätsanalysen. Nach der Verbesserung einer Symptomatik, sei nicht unbedingt zu erwarten, dass die Gehirnaktivität nach dieser Besserung der eines Gesunden entspräche, da für die Besserung kompensatorische Prozesse verantwortlich sein könnten, weshalb Untersuchungen über einen bloßen Vergleich einer klinisch auffälligen Gruppe mit gesunden Kontrollprobanden hinausgehen sollten (Kessler et al., 2011). In den hier vorgelegten Studien wurden nicht nur hoch belastete Tinnitusbetroffene mit gesunden

Kontrollprobanden verglichen, sondern auch mit niedrig belasteten Tinnitusbetroffenen, wodurch Rückschlüsse auf kompensatorische Prozesse möglich sind. So zeigte sich in Studie 2, dass Emotionsregulationsstrategien, wie das *Reappraisal*, eine Rolle bei niedriger Belastung spielen könnten. Im Sinne von Kessler et al. (2011) wurde zusätzlich zu den Gruppenvergleichen und dem Berechnen von Korrelationen, in Studie 1 eine Konnektivitätsanalyse durchgeführt.

3.2 Übereinstimmende Ergebnisse aus Studie 1 und 2

Vergleicht man die Ergebnisse von Studie 1 und 2 miteinander, so scheinen in beiden Studien übereinstimmend frontale Areale und die Insula mit Tinnitusbelastung assoziiert zu sein. Die Aktivität im linken mittleren frontalen Gyrus war in beiden Studien bei hoch im Vergleich zu niedrig belasteten Tinnitusbetroffenen erhöht, wenn auch unterschiedliche Bereiche des linken mittleren frontalen Gyrus (BA 6 bzw. 10) involviert waren. Die Aktivität im rechten inferioren frontalen Gyrus korrelierte in beiden Studien mit der Tinnitusbelastung, auch hier waren unterschiedliche Bereiche beteiligt (Studie 1: BA 09, 46; Studie 2: BA 47). Ebenso korrelierte die Aktivität in der Insula in beiden Studien mit der Tinnitusbelastung. In Studie 1 war die Korrelation auf die linke Insula und in Studie 2 auf die rechte Insula beschränkt. In Studie 1 war die Aktivität in der rechten Insula allerdings auch höher bei hoch belasteten Tinnitusbetroffenen im Vergleich zu gesunden Kontrollprobanden in Reaktion auf tinnitusbezogene im Vergleich zu neutralen Wörtern. In beiden Studien war eher der zentrale Teil der Insula beteiligt. Die Metaanalyse von Kurth et al. (2010) berichtet allerdings keine differentiellen Funktionen der linken und rechten Insula. Auf die Bedeutung einer Aktivierung der zentralen Insula wurde in Studie 2 bereits eingegangen. Die besondere Rolle des Precuneus, der Amygdala und des Hippocampus konnte in keiner unserer Studien bestätigt werden, was im Einklang mit den Ergebnissen anderer Studien steht. Dagegen finden alle Studien, die einen Zusammenhang von neuronaler Aktivierung und Tinnitusbelastung untersuchten, Aktivierungen in frontalen Arealen. Die Hälfte der Studien findet eine Beteiligung der Insula (vgl. Tabelle 2).

3.3 Die Rolle des linken mittleren und des rechten inferioren frontalen Gyrus bei Tinnitus

In Anbetracht der Ergebnisse der ersten hier vorgelegten Studie wurde vermutet, dass der linke mittlere frontale Gyrus an der Aufrechterhaltung dysfunktionaler Gedanken über Tinnitus im Arbeitsgedächtnis beteiligt sein könnte. Auch in Studie 2 scheinen tinnitusbezogene Wörter von der hochbelasteten Gruppe emotional verarbeitet worden zu sein. Die Daten beider Studien sind also konsistent hinsichtlich der Annahme einer besonderen Rolle des linken mittleren frontalen Gyrus in der Aufrechterhaltung tinnitusbezogener Information im Arbeitsgedächtnis. Eine Reihe von Befunden zeigt, dass der rechte inferiore frontale Gyrus mit der Identifikation salienter Reize in Verbindung steht (Downar, Crawley, Mikulis & Davis, 2002; Hampshire, Thompson, Duncan & Owen, 2009; Hampshire, Chamberlain, Monti, Duncan & Owen, 2010).

3.4 Praktische Implikationen der Erforschung neuronaler Korrelate von Tinnitusbelastung

Aufgrund ihrer Assoziation mit Tinnitusbelastung, könnten der linke mittlere frontale Gyrus sowie der rechte inferiore frontale Gyrus sinnvolle Zielregionen für neuromodulatorische Ansätze, wie TMS oder tDCS, sein. So wurden in den letzten Jahren mehrere Studien zu neuromodulatorischen Behandlungsansätzen bei belastendem chronischen Tinnitus durchgeführt (Kleinjung, Langguth & Khedr, 2011), wobei die Modulierung der Aktivität frontaler Areale mit einer Reduktion von Tinnitusbelastung in Verbindung gebracht werden konnte (Faber, Vanneste, Fregni & De Ridder, 2011; Kleinjung, et al., 2008; De Ridder & Vanneste, 2012). Nicht nur neuromodulatorische Ansätze, sondern auch pharmakologische Ansätze könnten von Grundlageforschung zu neuronalen Prozessen bei Tinnitus profitieren. So wurde kürzlich versucht den Ansatz der Netzwerk-Pharmakologie (*network pharmacology*) auf den Bereich Tinnitus anzuwenden (Elgoyhen, Langguth, Vanneste & De Ridder, 2012). Dabei soll ein Verständnis der Topologie des Tinnitusnetzwerkes und seiner Knotenpunkte (hubs) die Auswahl geeigneter Medikamente zur Einwirkung auf dieses Netzwerk, sogenannter *multi-target drugs*, erleichtern (Elgoyhen et al., 2012).

3.5 Ausblick

Aus den hier vorgelegten Studien ergeben sich einige neue Ideen sowie Modifikationshinweise für zukünftige Studien. Ergänzend zu bildgebenden Studien, in denen das Ohrgeräusch mittels Lidocain kurzfristig unterdrückt wurde (Reyes et al., 2002; Mirz, Gjedde, Ishizu, & Brahe Pedersen, 2000) oder Patienten untersucht wurden, die das Ohrgeräusch mittels Augen- (Lockwood et al., 2001; Giraud et al., 1999) bzw. Kieferbewegungen (Pinchoff, Burkard, Salvi, Coad & Lockwood, 1998) modulieren konnten, fehlen Studien zur Veränderung neuronaler Aktivierungen nach kognitiv-behavioralen Interventionen. Wünschenswert wäre ein Studiendesign, in dem zwei hoch belastete Gruppen von Tinnitusbetroffenen (Treatment vs. Wartegruppe) vor und nach einer kognitiv-behavioralen Intervention verglichen werden. Da sich diese Behandlung in

Metaanalysen als effektiv zur Reduktion von Tinnitusbelastung erwiesen hat (Hesser et al., 2011), sollten korrelativ Veränderungen der Hirnaktivität gefunden werden. Dieses Vorgehen entspräche der Forderung von Kessler et al. (2011) nach längschnittlichen Designs. Da die persönliche Relevanz von Stimuli, wie in Studie 1 deutlich wurde, eine Rolle zu spielen scheint, sollten zukünftige Studien idiosynkratrisches Stimulusmaterial verwenden (z.B. individuell bedeutsame negative Gedanken über Tinnitus). Ein Vorgehen, dass auch für die Untersuchung depressiver Störungen vorgeschlagen wurde (Kessler et al., 2011).

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Neural correlates of tinnitus related distress: An fMRI-study

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ABSTRACT

Chronic tinnitus affects approximately 5% of the population. Severe distress due to the phantom noise is experienced by 20% of the tinnitus patients. This distress cannot be predicted by psychoacoustic features of the tinnitus. It is commonly assumed that negative cognitive emotional evaluation of the tinnitus and its expected consequences is a major factor that determines the impact of tinnitus-related distress. Models of tinnitus distress and recently conducted research propose differences in limbic, frontal and parietal processing between highly and low distressed tinnitus patients. An experimental paradigm using verbal material to stimulate cognitive emotional processing of tinnitus-related information was conducted. Age and sex matched highly ($n = 16$) and low ($n = 16$) distressed tinnitus patients and healthy controls ($n = 16$) underwent functional magnetic resonance imaging (fMRI) while sentences with neutral, negative or tinnitus-related content were presented. A random effects group analysis was performed on the basis of the general linear model. Tinnitus patients showed stronger activations to tinnitus-related sentences in comparison to neutral sentences than healthy controls in various limbic/emotion processing areas, such as the anterior cingulate cortex, midcingulate cortex, posterior cingulate cortex, retrosplenial cortex and insula and also in frontal areas. Highly and low distressed tinnitus patients differed in terms of activation of the left middle frontal gyrus. A connectivity analysis and correlational analysis between the predictors of the general linear model of relevant contrasts and tinnitus-related distress further supported the idea of a fronto-parietal-cingulate network, which seems to be more active in highly distressed tinnitus patients. This network may present an aspecific distress network. Based on the findings the left middle frontal gyrus and the right medial frontal gyrus are suggested as target regions for neuromodulatory approaches in the treatment of tinnitus. For future studies we recommend the use of idiosyncratic stimulus material.

1. Introduction

Tinnitus is the perception of sound in the absence of external noise (Møller, 2011). Approximately 5% of the population is affected by chronic tinnitus (Fabijanska et al., 1999; Palmer et al., 2002). However, only 20% of the afflicted individuals experience severe distress related to the phantom noise (tinnitus) (Davis and Rafaie, 2000; Andersson and Kaldo, 2004). Common problems related to tinnitus are sleeping difficulties, concentration problems, mood disturbances and hearing problems (Andersson and Kaldo, 2004). The amount of perceived distress cannot be predicted by the psychometrically measured qualities of the sound of the tinnitus

Abbreviation: ACC, anterior cingulate cortex; aMCC, anterior midcingulate cortex; ATQ, Automatic Thoughts Questionnaire; BA, Brodmann Area; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; dPCC, dorsal posterior cingulate cortex; DSM-IV, diagnostic and statistical manual of mental disorders (fourth edition); fMRI, functional magnetic resonance imaging; Gdys, generally negative sentences; GÜF, Geräuschüberempfindlichkeitsfragebogen (Questionnaire on Hypersensitivity to Sound); HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; HDT, highly distressed tinnitus patients; LDL, loudness discomfort level; LDT, low distressed tinnitus patients; LORETA, Low Resolution Brain Electromagnetic Tomography; LSD, least significant difference; MCC, midcingulate cortex; MML, minimal masking level; MR, magnetic resonance; MRI, magnetic resonance imaging; Neu, neutral sentences; pACC, posterior anterior cingulate cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PHQ-D, German version of the Patient Health Questionnaire; RI, residual inhibition; RSC, retrosplenial cortex; rTMS, repetitive transcranial magnetic stimulation; sACC, subgenual anterior cingulate cortex; SAM, Self-Assessment Manikin; scACC, subcallosal anterior cingulate cortex; STI, Structured Tinnitus Interview; tDCS, transcranial direct current stimulation; Tdys, tinnitus-related sentences; TE, echo time; TMS, transcranial magnetic stimulation; TQ, Tinnitus Questionnaire; TR, repetition time; VLPFC, ventrolateral prefrontal cortex.

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(Henry and Meikle, 2000; Hiller and Goebel, 2007). It is commonly assumed that negative cognitive emotional evaluation of tinnitus and its expected consequences is a major factor determining the impact of tinnitus-related distress. The Neurophysiological Model by Jastreboff (Jastreboff et al., 1996) proposes that distress emerges if the initial perception of the tinnitus is associated with negative evaluation (*e.g.* "*I am going deaf*"). This process activates the limbic and concordantly the autonomic nervous system. In chronic tinnitus, the tinnitus sound is supposed to activate these systems without conscious evaluation through conditioning processes. According to the model, habituation will be impeded due to the emotional significance of the perception, resulting in the experience of distress and the development of psychological symptoms.

Recently, an important extension of the Neurophysiological Model, termed the Global Brain Model, has been proposed (Schlee et al., 2011). According to the model, reduced sensory input due to damage in the hearing system decreases inhibitory mechanisms in the central auditory system and finally enhances excitability of the auditory cortices. The model further states that activity in the auditory cortex is modulated by a fronto-parietal-cingulate network, which is supposed to be more active in highly distressed tinnitus patients. Key structures in this network are: the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex, the anterior cingulate cortex (ACC) and the precuneus/posterior cingulate cortex (PCC).

De Ridder (2011) assumes an aspecific network consisting of the amygdala, the ACC and the anterior insula as being responsible for tinnitus-related distress. This assumption has been tested on resting-state EEG data of highly and low distressed tinnitus patients as well as healthy controls (De Ridder et al., 2011). The data was analyzed with a group blind source separation analysis, a method similar to the independent component analysis in fMRI (see Schmithorst and Holland, 2004 for details). One component was identified in which the brain activity in two frequency bands (14–18 Hz, 22–26 Hz) differed between highly and low distressed tinnitus patients. That component consisted of the medial frontal gyrus, rectal gyrus and the ACC (Brodmann Area (BA) 11, 25), the middle frontal gyrus (BA 11), inferior frontal gyrus (BA 47), parahippocampal gyrus (BA 28/34) and the insula (BA 13). Furthermore a positive correlation in the alpha and beta range of these regions with tinnitus-related distress was found (De Ridder et al., 2011). Distress in relation to pain has also been associated with activity of the prefrontal cortex, the insula and the ACC (Moisset and Bouhassira, 2007), thus supporting the assumption of an aspecific distress network (De Ridder et al., 2004).

There is only one more recent resting-state EEG-study that compared highly and low distressed tinnitus patients. Anatomic locations were analyzed using Low Resolution Brain Electromagnetic Tomography (LORETA). Various emotion-related areas showed more synchronized activity in highly distressed tinnitus patients, including the subcallosal ACC (scACC), the anterior insula cortex, the parahippocampal area and the amygdala. Less synchronized activity was shown in the precuneus, PCC and DLPFC and ventrolateral prefrontal cortex (VLPFC). A stepwise backward regression analysis showed that the scACC, the parahippocampal area, the PCC and the DLPFC contributed significantly to tinnitus-related distress (Vanneste et al., 2010b). Thus, Vanneste et al. (2010b) did not confirm the role of the precuneus in the distress network as suggested by the Global Brain Model. However, disadvantages of LORETA-analyses in comparison to fMRI are a lower spatial resolution and a restriction to cortical gray matter and the hippocampus (Mulert et al., 2004). A correlation between the strength of inflow to the temporal cortices and tinnitus-related distress was found in a resting-state study that used Magnetoencephalography. The temporal cortices received input from the prefrontal cortex (PFC), cuneus, precuneus and the PCC (Schlee et al., 2009). Further evidence for the importance of the proposed brain regions in the tinnitus distress network comes from studies using transcranial magnetic stimulation (TMS). It has been found that a good response to repetitive TMS (rTMS) as measured by the Tinnitus Questionnaire (TQ) (Hallam, 1996; Goebel and Hiller, 1998) correlates with tinnitus associated activity in the ACC (Plewnia et al., 2007). In another study, a group of tinnitus patients was treated either with low-frequency temporal rTMS or a combination of low-frequency temporal and high-frequency prefrontal rTMS. Directly after therapy both groups improved regarding their level of tinnitus-related distress as measured by the TQ. After three month follow-up, an advantage of the combined treatment was shown (Kleinjung et al., 2008). This study indicates a potential role of the PFC in the distress network of tinnitus patients. Judging from these studies, regions of interest in a fronto-parietal-limbic network seem to be the ACC, PCC, insula, amygdala, parahippocampal gyrus (limbic), the PFC and the precuneus (parietal cortex). Complementary to the existing resting-state studies, we wanted to activate distress-related brain regions by tinnitus-related stimulus material to determine how highly and low distressed tinnitus patients differ in their activation of the network. An understanding of the distress network and its mechanisms could help to identify targets for neuromodulatory approaches like TMS in the therapy of tinnitus.

The Neurophysiological Model states a negative initial evaluation of the tinnitus as a crucial condition for the development of tinnitus annoyance (Jastreboff et al., 1996). Negative evaluations are also a maintaining factor of tinnitus-related distress as part of a vicious circle, which should lead to stress, heightened tinnitus perception and attention focus on the phantom sound (Mertin and Kröner-Herwig, 1997). A study conducted on 81 tinnitus sufferers, who among others filled in the Tinnitus Cognitions Questionnaire (Wilson and Henry, unpublished) and the Automatic Thoughts Questionnaire (ATQ) (Hollon and Kendall, 1980), found that highly distressed tinnitus patients had a greater tendency to engage in tinnitus-specific negative cognitions than low distressed individuals, while there were no differences in the ATQ as a measure of general dysfunctional cognitions (Henry and Wilson, 1995). Thus only the amount of negative tinnitus-related cognitions differentiated between highly and low distressed tinnitus afflicted individuals. Hence, tinnitus-related negative sentences are expected to represent an adequate stimulus material to activate the brain areas involved in tinnitus annoyance. Positive results regarding the adequacy of verbal stimuli to induce emotional processing were obtained from studies examining healthy subjects and psychopathology. Healthy subjects showed higher activations as measured by blood oxygen level dependent (BOLD) fMRI in the left precuneus and left ACC when reading emotional compared to neutral sentences (Medford et al., 2005). Another experiment showed that negative sentences activated the hippocampus and the middle frontal gyrus to a higher extent when participants were instructed to identify the emotion compared to the gender in visually presented sentences (Bleich-Cohen et al., 2006). Furthermore, it has been shown that audiological presented worry-sentences compared to neutral sentences elicit greater brain activation in various brain regions including the insula, parahippocampal gyrus, ACC, PCC, frontal gyrus and precuneus in patients with generalized anxiety disorder before an anxiety reducing treatment with citalopram (Hoehn-Saric et al., 2004). Thus, emotional sentences seem to be adequate stimuli for the examination of regions of interest in tinnitus patients. The aim of this study was to determine neural correlates of tinnitus-related distress using fMRI.

We hypothesized that highly distressed tinnitus patients (HDT) evaluate tinnitus-related sentences (Tdys) as being more negative, arousing and relevant than neutral (Neu) sentences and also more relevant than generally negative sentences (Gdys). In addition HDT should evaluate Tdys more negative, arousing and relevant than low distressed tinnitus patients (LDT) and healthy controls (HC). Regarding the emotional processing of tinnitus-related verbal material, we expected HDT to show higher activations of the precuneus, limbic and frontal brain regions to Tdys than in response to Neu or Gdys. Those differences were expected to be higher in HDT compared to LDT and HC and should correlate with tinnitus-related distress. We further aimed to explore the functional connectivity of those brain regions that show to be more active in HDT compared to LDT.

2. Materials and methods

2.1. Sample

Participants were recruited via newspapers, flyers, the homepage of the German Tinnitus League and word of mouth. Exclusion criteria were a current major depressive episode, hyperacusis, age above 70 years, no German mother tongue, any counter indications to MR-methodology (e.g. pacemaker), current treatment with psychotropic drugs, days without tinnitus perception, a tinnitus duration of less than 12 months, perception of tinnitus only in total silence, residual-inhibition > 1 min and an actual hearing loss. The cutoff for high tinnitus-related distress was a score of ≥31 (moderate annoyance) in the German version of the TQ (Goebel and Hiller, 1998). The final sample consisted of sixteen HDT, LDT and HC ($N = 48$), matched by age and sex. HDT had higher levels of tinnitus-related distress, depression, anxiety and hypersensitivity to sound in comparison to LDT and HC. Additionally, HDT had poorer vocabulary than LDT (see Table 1 for details). The three groups did not differ with regard to hearing loss ($F(2, 45) = 1.42$, $p = 0.25$; see Fig. 1). The study had been approved by the ethics committee of the medical department of the University of Goettingen and all participants gave written informed consent to participate in the study.

2.2. Experimental design

The emotional sentence task comprised three conditions (independent variable); Tdys (*e.g. I will never get rid of the noise*), Gdys (e.g. *I often feel sorry for myself*) and Neu (*e.g. Regularly, I look at my watch*). In each condition 15 sentences were included, which were randomly presented during the task (see the supplementary material for a list of the stimulus material). Thus, the study had a 3 × 3 quasi-experimental design with the within-factor sentence type (Tdys, Gdys, Neu) and the between-factor group (HDT, LDT, HC). Brain activity in the defined areas served as dependent variable.

Inside the MRI-scanner stimuli were presented on a set of MR-suited LCD-goggles with a resolution of 800 × 600 (Resonance Technology, Northridge, CA, USA). If necessary, corrective lenses were combined with the goggles to ensure corrected to normal vision. All participants wore headphones for noise protection and communication with the experimenter. The sentences were presented randomly in an event-related design. Each sentence was presented for 8 s preceded by a fixation cross for 10, 12 or 14 s. The participants rated the personal relevance of each sentence (for details see below). The participants underwent two more experiments in the MRI, which will not be discussed here, so that the total scan-time was approximately 60 min.

The tinnitus-related sentences were based on a German questionnaire addressing dysfunctional beliefs related to tinnitus. It consists of 33 negative statements about tinnitus as frequently heard in clinical practice (Hiller, 1999, unpublished; please see the supplementary material for an item list). Generally negative sentences were derived from the subscales *negative view of self* (Negative Selbstbewertung) and *dependency on the opinions of others* (Abhaengigkeit) of a German questionnaire addressing irrational beliefs (Fragebogen irrationaler Einstellungen) (Klages, 1989). It has been shown previously that psychological therapy aimed at the reduction of tinnitus distress did not modify scores on these scales (Rienhoff et al., 2002), and therefore, items from these subscales are expected to be unrelated to tinnitus distress. Thus, Gdys were included in the study to control for a general effect of negative verbal material. The last word of each neutral sentence consisted of a neutrally valenced word taken from a semantic atlas which contains a list of nouns, adjectives, verbs and information about their emotional content (e.g. valence) (Schwibbe et al., 1994). Then, each word was embedded in a context that described activities of daily living. All sentences were adapted to the trial, to match the number of words between sentence categories.

2.3. Assessment of psychosocial variables

2.3.1. Tinnitus-related distress

To allocate participants to the high and low tinnitus-related distress group, the TQ (Goebel and Hiller, 1998; Hallam, 1996) was used. The TQ is a self-report rating scale which assesses tinnitus-related distress with 52 items on the following subscales: emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances and somatic complaints. A score of 0–30 represents mild tinnitus annoyance, 31 to 46 corresponds to moderate annoyance, between 47 and 59 tinnitus-related distress is considered severe and a score of 60 and above

Table 1
Description of the groups and characterizing variables.

	HDT ($n = 16$; 14♂)		LDT ($n = 16$; 14♂)		HC ($n = 16$; 14♂)		HDT vs. LDT df = 30	HDT vs. HC df = 30
	Mean	SD	Mean	SD	Mean	SD	*t*-value	*t*-value
Age	52.9	11.9	53.9	9.9	52.5	9.6	−0.24	0.11
HADS A	8.0	3.5	4.4	3.4	2.7	2.3	2.93**	5.09***
HADS D	6.8	3.4	3.4	3.7	2.2	2.4	2.69*	4.37***
VT	19.9	5.5	24.4	4.1	21.6	4.1	−2.69*	−1.01
GÜF	13.5	8.3	6.6	6.6	2.8	2.3	2.58*	4.98***
TQ[a]	41.3	7.0	16.1	7.1			10.10***	
dB (HL)	41.8	21.4	51.1	19.6			−1.29	

HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls, HADS = Hospital Anxiety (A) and Depression (D) Scale, VT = Vocabulary Test, TQ = Tinnitus Questionnaire, dB = tinnitus loudness in decibles, HL = hearing level, ♂ = male, df = degrees of freedom, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a] Due to missing data on the day of the MRI-scan, the missing TQ-score of 4 participants (1 HDT, 3 LDT) was replaced with the TQ-score from the TQ, that had been filled in after the telephone screening.

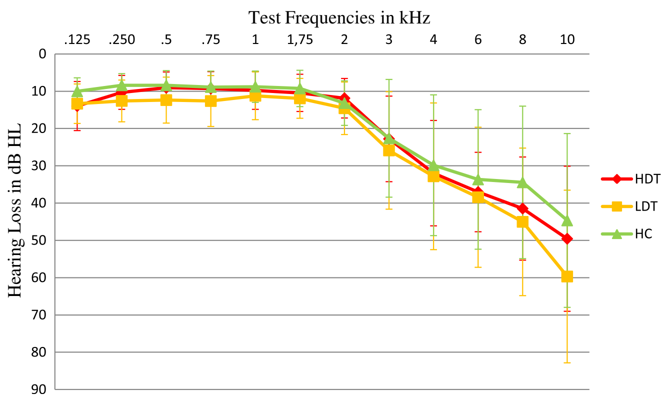

Fig. 1. Average hearing loss per group; *x*-axes: hearing loss in dB HL, *y*-axis: test-frequencies in kHz. HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls.

corresponds to very severe tinnitus annoyance. The test-retest reliability for the TQ global score is $r_{tt} = 0.94$ and ranges between $r_{tt} = 0.86–0.93$ for the subscales (Hiller et al., 1994).

2.3.2. Assessment of exclusion criteria

To exclude a current depressive episode and psychotropic medication the German version of the Patient Health Questionnaire (PHQ-D) was used (Graefe et al., 2004). The PHQ-D is a screening instrument for mental disorders screening for somatization disorder, anxiety disorders, depression, eating disorders and alcohol abuse using the diagnostic criteria of the DSM-IV. Furthermore it includes items to assess overall psychosocial functioning, life events, stressors, medication against stress, anxiety or depression and information concerning menstruation, pregnancy and giving birth (Loewe et al., 2002). The PHQ-D is a valid and well accepted diagnostic instrument for use in research and clinical practice (Graefe et al., 2004).

To exclude certain tinnitus characteristics; hyperacusis, diagnosed hearing loss, acute tinnitus, days without tinnitus and tinnitus perception that occurred only in total silence, the Structured Tinnitus Interview (STI) was used (Goebel and Hiller, 2001). The STI assesses anamnestic information about the tinnitus, associated symptoms (hearing loss, hyperacusis, vertigo), aetiological factors, tinnitus-related distress and information about previous therapies. The STI has a test-retest-reliability of $r_{tt} = 0.90$ and an internal consistency of $\alpha = 0.92$.

To further examine exclusion criteria related to tinnitus and to characterize the tinnitus, an audiological examination was conducted by trained audiologists, which consisted of pure tone audiometry, tinnitus pitch and loudness matching, determination of the loudness discomfort level (LDL), minimal masking level (MML) and residual inhibition (RI). LDL, MML and RI are the subject of another study and will not be discussed in this study. Hearing loss was defined by the Guidelines *on Non-Physician Care and Medical Aids* (Heil-und Hilfsmittelrichtlinien) as a loss of ≥30 dB HL in two frequencies between 0.5 kHz and 3 kHz on the better hearing ear (bilateral) or a loss of ≥30 dB HL at 2 kHz (see Seidler, 1996).

2.3.3. Sample characterization

General distress was assessed by means of the German version of the Hospital Anxiety and Depression Scale (HADS) (Herrmann et al., 1995). It is a well-established 14-item instrument to assess anxiety and depression with an internal consistency of $\alpha = 0.80$ for the anxiety subscale and $\alpha = 0.81$ for the depression subscale with a convergent validity of $r = 0.65$ for the anxiety and $r = 0.70$ for the depression subscale. It was specifically designed to assess anxiety and depression in patients with chronic diseases (Herrmann et al., 1995).

Susceptibility to sounds was assessed by the Questionnaire on Hypersensitivity to Sound (Geräuschüberempfindlichkeitsfragebogen; GÜF) (Nelting and Finlayson, 2004). The GÜF is a self-administered questionnaire which consists of three subscales; cognitive reaction to hypersensitivity to sounds, somatic behavior and emotional reaction to external noise. The maximum score of the GÜF is 45, a score of 0–9 represents mild hypersensitivity to sounds, 10 to 15 corresponds to moderate hypersensitivity, between 16 and 23 hypersensitivity to sounds is considered severe and very severe between 24 and 45. Internal consistency of the subscales ranges from $r = 0.77$ to $r = 0.82$. The correlation between the severity grading of the GÜF and an expert consensus that was based on a structured interview was $r = 0.82$.

2.3.4. Behavioral data

All verbal stimuli were rated on a computerized version of the Self-Assessment Manikin (SAM) (Bradley and Lang, 1994; Barke et al., 2011) according to valence and arousal. The nine-point valence scale ranged from "very negative" (1) to "very positive" (9). The arousal scale ranged from "not arousing" (1) to "very arousing" (9).

Inside the MRI, the participants rated the personal relevance of each sentence during its presentation via button press on a fiber optic response pad. The pad consisted of four colored buttons. Only the three buttons on the left were used in the experiment. Participants were instructed to press the corresponding button with the index (button 1 = not relevant), middle (button 2 = somewhat relevant) or ring finger (button 3 = very relevant) of their right hand.

2.3.5. Control variables

The Vocabulary subtest of the Hamburger Wechsler Intelligence Test (Tewes, 1991) was used to assess each participant's word pool, since novelty of words could affect neural correlates of verbal stimulus material (Saykin et al., 1999). Differences in vocabulary between groups could act as a confounding variable.

2.4. Image acquisition

MR imaging was performed at 3 T (Siemens Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) using a standard 8-channel phased-array head coil (due to head-size a 12-channel coil had to be used for one participant). All participants wore headphones for noise protection. Initially an anatomical 3D T1-weighted dataset was acquired (Turbo fast low angle shot (Turbo FLASH), echo time (TE): 3.26 ms, repetition time (TR): 2250 ms, inversion time: 900 ms, flip angle 12°), which covered the whole head at $1 \times 1 \times 1$ mm^3 isotropic resolution. The functional datasets were acquired using T2*-weighted gradient-echo echo-planar imaging (TE: 36 ms, TR: 2000 ms, flip angle 90°, 22 slices of 4 mm thickness at an in-plane resolution of 2×2 mm^2). 455 whole brain volumes were recorded within one functional run.

2.5. Procedure

All individuals applying for the study underwent a telephone screening of approximately 20 min consisting of questions about exclusion criteria, demographic information and the German Version of the STI (Goebel and Hiller, 2001). Questionnaires were sent to all participants who passed the screening. The participants completed the PHQ-D (Loewe et al., 2002), the TQ (Goebel and Hiller, 1998), the HADS (Herrmann et al., 1995), the GÜF (Nelting and Finlayson, 2004) and a questionnaire to further assess counter-indications to MRI. Before entering the scanner, all participants received a training to become familiar with the tasks. The training consisted of 10 neutral sentences in the form of "I often talk about…" (e.g. animals). The participants judged the personal relevance of each sentence by pressing one of three keyboard buttons with their right hand (1 = not relevant, 2 = somewhat relevant, 3 = very relevant). After the pre-training the participants completed the experiment while they were lying in the MRI-scanner. The experiment consisted of three tasks, the emotional sentence task, a masking paradigm and an emotional Stroop task. However, only the results of the emotional sentence task will be reported. Immediately after the scanning procedure the participants rated all verbal stimuli according to valence and arousal with the computerized SAM-version and filled in the TQ for a second time, to measure the amount of tinnitus distress on the day of the assessment. The vocabulary test was conducted at a later date via telephone, since the participants could be exhausted after the MRI- and rating-procedure.

2.6. Statistical analysis

2.6.1. Behavioral data

Regarding the ratings of relevance, valence and arousal, three 3 × 3 repeated measures ANOVAs with the between-subject factor group (HDT, LDT, HC) and the within-subject factor sentence type (Tdys, Gdys, Neu) were calculated. In case of a violation of the sphericity assumption, Greenhouse-Geisser corrections were performed. LSD-post-hoc-tests were performed for further analyses and p was set at 0.05.

2.6.2. Functional images

The fMRI data processing was conducted with Brain Voyager QX Software version 2.0.8 (Brain Innovation, Maastricht, The Netherlands) respectively version 2.2 for the definition of the predictors of the connectivity analysis. Standard preprocessing steps included 3D motion correction, slice scan-time correction, temporal filtering (linear trend removal and high pass filtering) and spatial smoothing with a Gaussian kernel (full width at half maximum 8 × 8 × 8 mm^3). A random effects group analysis was performed on the basis of the general linear model. The effects of the 8 s presentation of the sentences were convolved with the canonical hemodynamic response function and analyses of planned contrasts were performed. Correction for multiple comparisons was based on cluster threshold estimation (Forman et al., 1995; Goebel et al., 2006). For the within group analysis the uncorrected cluster threshold was set at $p = 0.01$. For the between-group analysis the cluster threshold was set at $p = 0.05$. To determine the minimum cluster size required to yield a maximum error rate at the cluster level of $p > 0.05$, Monte Carlo simulations (1000 iterations) were performed on the basis of the number of activated voxels and the estimated smoothness of the map. Activations were identified by nearest coordinates in the Talairach Demon (Lancaster et al., 1997, 2000). Activations located in the cingulate gyrus were allocated to the subdivisions of the cingulate gyrus according to the Four-Region Neurobiological Model. (Vogt et al., 2003, 2004; Vogt, 2005). For connectivity and correlational analysis only tinnitus patients were included. A seed based connectivity analysis was performed on basis of the general linear model by using the variation in time of the target region as predictor, the signal of the ventricles and the global brain signal were included as confound predictors (Weissenbacher et al., 2009). Firstly, a connectivity analysis was performed for the HDT group. Secondly, the model of the highly distressed group was contrasted with the model of the low distressed group, to determine which parts of the distress network correlated higher in HDT as compared to LDT. Therefore we applied a mask of the results for the HDT group to the general linear model in which both groups were contrasted with each other. For the connectivity analysis and correlational analysis the uncorrected cluster threshold was set at $p = 0.01$. For correlational analysis, the predictors of the general linear model for the two contrasts Tdys > Neu and Tdys > Gdys were extracted for all tinnitus subjects (LDT and HDT). Then these values were correlated with the individual TQ-scores.

3. Results

3.1. Behavioral data

3.1.1. Ratings of valence, arousal and relevance

We hypothesized that HDT evaluate Tdys more arousing, negative and relevant than Neu and more relevant than Gdys. In addition HDT should evaluate Tdys more negative, arousing and relevant than LDT and HC. To test whether HDT evaluate Tdys more negative than Neu and also more negative in comparison to LDT and HC, an analysis of variance and post-hoc LSD-tests were performed. Valence ratings (Fig. 2) showed no main effect for group ($F(2, 42) = 1.25$, $p = 0.507$) and a main effect of sentence type ($F(1.65, 69.15) = 66.02$, $p < 0.001$), however was confirmed. No group × sentence type interaction ($F(3.29, 69.15) = 1.14$, $p = 0.342$) (see Table 2 for details) was found. LSD-post-hoc-tests demonstrated that all participants rated tinnitus-related and generally negative sentences as being more negative than neutral sentences ($p < 0.001$).

To test for higher arousal scores in HDT, an analysis of variance was performed. Ratings of arousal also (Fig. 3) showed a main effect for sentence type ($F(2, 84) = 24.8$, $p < 0.001$) and no main effect for group ($F(2, 42) = 0.53$, $p = 0.59$), nor a group × sentence type interaction ($F(4, 84) = 1.4$, $p = 0.16$). LSD-post-hoc-tests showed significant differences within each group between Neu and Gdys and between Neu and Tdys ($p < 0.05$). All participants rated Tdys and Gdys as being more arousing than neutral sentences (see Table 2 for details).

Ratings of personal relevance (Fig. 4) showed no main effect for group ($F(2, 44) = 0.48$, $p = 0.621$). A main effect for sentence type ($F(1.75, 76.96) = 40.01$, $p < 0.001$) and a group × sentence type interaction ($F(3.49, 76.96) = 3.38$, $p < 0.05$) however were confirmed. LSD-post-hoc-tests showed that HDT evaluated Tdys as being more personally relevant than Gdys ($p = 0.006$). There was no difference between Neu and Tdys in HDT ($p = 0.208$). LDT and HC

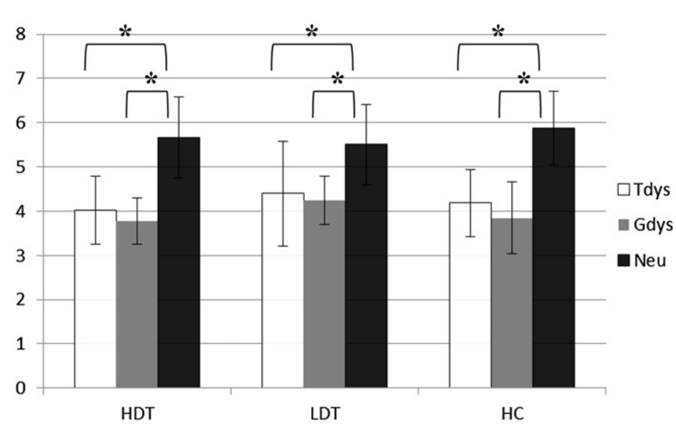

Fig. 2. SAM-ratings of valence (9 point scale). Lower values indicate a more negative evaluation. Tdys = tinnitus-related sentences, Gdys = generally negative sentences, Neu = neutral sentences, HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls.

Table 2
Behavioral data.

	HDT ($n = 16$; 14♂)		LDT ($n = 16$; 14♂)		HC ($n = 16$; 14♂)		ANOVA F		
	Mean	SD	Mean	SD	Mean	SD	G	ST	G × ST
Val Tdys	4.0	0.8	4.4	0.5	4.2	0.9			
Val Gdys	3.8	1.2	4.2	0.5	3.8	0.9	1.25	66.02***	1.14
Val Neu	5.7	0.8	5.5	0.8	5.9	0.8			
Arou Tdys	3.7	2.1	2.6	1.5	2.9	1.6			
Arou Gdys	3.2	2.1	2.7	1.4	3.2	2.1	0.53	24.8**	1.71
Arou Neu	1.8	1.2	1.7	1.0	2.1	1.5			
Rel Tdys	1.9	0.35	1.7	0.5	1.6	0.4			
Rel Gdys	1.6	0.3	1.6	0.2	1.6	0.29	0.48	40.01***	3.38*
Rel Neu	2.0	0.4	2.1	0.3	2.4	0.4			

Val = Valence; Arou = Arousal; Rel = Relevance; HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls; Tdys = tinnitus-related sentences; Gdys = generally negative sentences; Neu = neutral sentences; G = Group; ST = Sentence Type; GST = Interaction: Group × Sentence Type; *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$.

evaluated Neu as being more personally relevant than Gdys ($p < 0.001$) and Tdys ($p < 0.001$). Furthermore, HDT and HC differed in the personal relevance ratings of Tdys ($p < 0.05$); highly distressed tinnitus patients found Tdys more personally relevant than HC. The difference in the evaluation of Tdys between HDT and LDT did not reach significance ($p = 0.106$) (for details see Table 2).

3.2. FMRI data

3.2.1. Within group analysis: highly distressed tinnitus patients

Differences in BOLD-response to different sentence types within HDT were determined to test whether these patients showed a stronger neural response to Tdys as compared to Neu and Gdys in the precuneus, limbic and frontal brain areas (Fig. 5). HDT showed stronger neural responses to Tdys compared to the other two stimuli types in frontal regions, dorsal PCC (dPCC), retrosplenial cortex (RSC) and the precuneus. See Table 3 for details about the hypothesized regions.

3.2.2. Analysis of differences between HDT and HC

Neural activity to Tdys in contrast to Neu was compared between HDT and HC (please see the supplementary material for the results of Gdys > Neu) to test whether highly distressed tinnitus patients showed higher activation levels BOLD signal in the precuneus, limbic and frontal regions. HDT showed stronger activations in various parts of the cingulate gyrus and the insula. They also showed higher activations in parts of the DLPFC, orbitofrontal cortex and left middle frontal gyrus (BA 08). Tdys were contrasted with the activity to Gdys and compared between HDT and HC. HDT showed a stronger activation in the left superior frontal gyrus as part of the DLPFC (Table 4).

3.2.3. Analysis of differences between HDT and LDT

HDT showed a stronger activation in the left middle frontal gyrus (BA06) than LDT to Tdys compared to Neu (Fig. 6). There were no differences between the two groups when the activity to Tdys was contrasted with the activity to Gdys (please see the supplementary material for the results of Gdys > Neu).

3.2.4. Connectivity analysis

To test whether the cluster in the left middle frontal gyrus was functionally connected to the precuneus, limbic areas and frontal regions, a seed based connectivity analysis was performed. Correlations between the seed region and the posterior ACC (pACC), midcingulate cortex (MCC), RSC and insula were found as well as correlations with the precuneus and frontal regions. Those correlations were higher for HDT in limbic, frontal and parietal regions, such as the ventral PCC, insula, RSC and medial frontal gyrus (for details see Table 5 and Fig. 7).

3.2.5. Correlational analysis

The predictors of the general linear model for the two contrasts Tdys > Neu and Tdys > Gdys were extracted for all tinnitus subjects (LDT and HDT). Then these values were correlated with the individual TQ-scores to test, whether tinnitus distress correlated with activity in the precuneus, limbic and frontal regions. Tinnitus

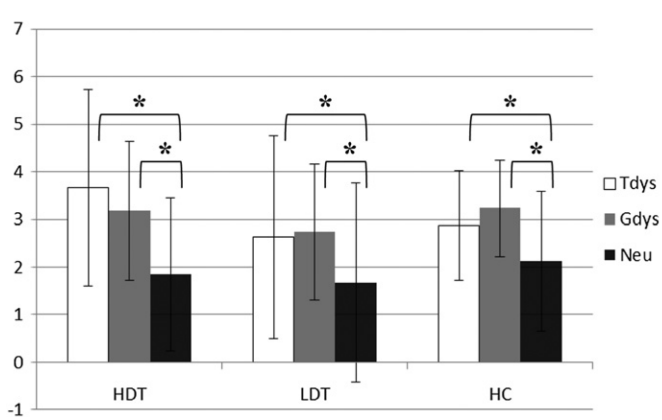

Fig. 3. SAM-ratings of arousal (9 point scale). Higher values indicate a higher arousal. Tdys = tinnitus-related sentences, Gdys = generally negative sentences, Neu = neutral sentences, HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls.

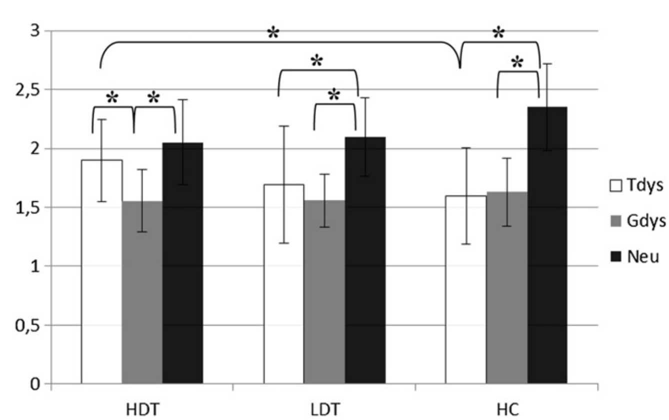

Fig. 4. SAM-ratings of relevance (3 point scale). Higher values indicate a higher relevance. Tdys = tinnitus-related sentences, Gdys = generally negative sentences, Neu = neutral sentences, HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients, HC = healthy controls.

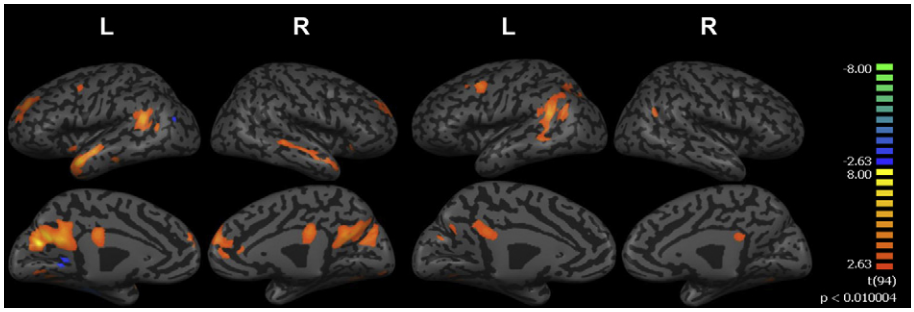

Fig. 5. Within group results of HDT. HDT = highly distressed tinnitus patients; the four pictures on the left represent the contrast: tinnitus-related sentences vs. neutral sentences, the four pictures on the right represent the contrast tinnitus-related sentences vs. generally negative sentences.

distress correlated positively with a higher activity to Tdys in various hypothesized regions as the DLPFC, medial and middle frontal gyrus, the insula, anterior MCC (aMCC) and the pACC (see Table 6 for details).

4. Discussion

The aim of the study was to determine neural correlates of tinnitus-related distress and to explore the distress network in chronic tinnitus patients. Therefore, we conducted an emotional sentence task and compared the neural activity, measured by BOLD fMRI signal, to tinnitus-related sentences to the activity elicited by neutral sentences and generally negative sentences. We expected lower valence ratings, higher arousal ratings and higher relevance ratings for tinnitus-related sentences within the group of highly distressed tinnitus patients in comparison to neutral sentences and in comparison to low distressed tinnitus patients and healthy controls. Contrary to our hypothesis we did not find differences between the groups for arousal and valence, though all groups rated tinnitus-related sentences to be more negative and arousing in comparison to neutral sentences. However, highly distressed tinnitus patients evaluated tinnitus-related sentences more relevant than generally distressing sentences. More importantly, we found higher relevance ratings for tinnitus-related sentences in highly distressed tinnitus patients in comparison to healthy controls and a trend for higher relevance of tinnitus-related sentences in comparison to low distressed tinnitus patients. Hence, it seems that the relevance of tinnitus-related negative thoughts is the differentiating factor between the groups. On a neural basis we expected highly distressed tinnitus patients to show higher activations in response to tinnitus-related sentences than to neutral sentences and generally negative sentences in frontal brain regions, limbic areas and the precuneus. Indeed, we found support for this hypothesis in our data. In comparison to previous studies, we were able to confirm some of the results of De Ridder et al. (2011) as we also identified the middle, medial and inferior frontal gyrus, the insula and the ACC as parts of the distress network in the high distress group. More importantly the right medial frontal gyrus and left insula were more active in the distress network of highly distressed tinnitus patients than in low distressed tinnitus patients. We however failed to find a significant contribution of the rectal gyrus and the parahippocampal gyrus. In accordance with the results of Vanneste et al. (2010b) we found correlations with tinnitus distress and the DLPFC. The PCC was more active in the

Table 3
Within group results in HDT: Selection of activations of the hypothesized regions in whole brain analysis. A table with all activations can be found in the supplementary material.

Contrast	Region	BA	Peak voxel			*t*-value	Voxels (mm^3)
			x	*y*	*z*		
Tdys > Neu	R Inferior frontal gyrus	47	42	20	−5	3.67	684
	R Medial frontal gyrus	10	9	44	10	3.59	1604
	L Medial frontal gyrus	09	−12	41	19	3.41	819
	L Middle frontal gyrus	06	−36	2	46	3.23	464
	R Superior frontal gyrus	09	6	56	25	4.35	4048
	L Superior frontal gyrus	08	−18	47	38	3.68	3827[a]
	L Superior frontal gyrus	10	−24	56	13	2.90	
	L Superior frontal gyrus	09	−18	47	28	5.23	
	R Precuneus	31	12	−70	28	4.32	3753
	L Precuneus	31	−6	−64	22	7.25	4189
	R RSC	29	3	−46	16	4.51	2353
	L dPCC	23	−3	−22	28	4.77	711
Tdys > Gdys	R Precuneus	31	18	−70	28	2.96	257
	L Precuneus	31	−3	−67	25	3.11	433
	L Precuneus	31	0	−49	34	2.75	110
	L Precuneus	07	−24	−67	37	3.11	719
	L Inferior frontal gyrus	09	−42	14	22	3.14	57
	L Middle frontal gyrus	06	−33	11	47	4.18	3121
	R Superior frontal gyrus	09	15	44	31	3.65	817
	R RSC	29	3	−43	10	3.34	85
	L dPCC	23	−3	−34	28	3.76	1114

Tdys = tinnitus-related sentences; Neu = neutral sentences; Gdys = generally negative sentences; R = right; L = left; RSC = retrosplenial cortex; dPCC = dorsal posterior cingulate cortex; BA = Brodman area.

[a] Refers to the total size of the L Superior frontal gyrus in the cluster.

Table 4
Between group analysis of HDT vs. HC.

Contrast	Cluster	Region	BA	Peak voxel			t-value	Cluster size (mm^3)
				x	y	z		
Tdys > Neu	1	R pACC	32	9	44	7	2.73	37351
		R Medial frontal gyrus	10	15	56	6	2.94	
		R Middle frontal gyrus	46	48	35	19	3.36	
		R Middle frontal gyrus	09	48	26	34	2.47	
		R Superior frontal gyrus	09	45	38	29	3.36	
		R Superior frontal gyrus	10	27	60	16	3.08	
		L/R pACC	24	0	32	7	2.48	
		L/R aMCC	24	0	23	16	2.74	
		L sACC	24	−6	23	−2	2.62	
		L Claustrum		−24	20	−2	2.68	
		L Inferior frontal gyrus	47	−21	17	−17	2.51	
		L Insula	13	−33	26	19	2.50	
		L Lentiform nucleus		−18	5	4	2.91	
		L Medial frontal gyrus	10	−6	60	16	2.70	
		L Medial frontal gyrus	09	−12	38	19	3.67	
		L Middle frontal gyrus	08	−21	32	37	3.23	
		L Middle frontal gyrus	10	−27	44	22	3.40	
		L Middle frontal gyrus	09	−27	32	25	2.11	
		L Middle frontal gyrus	46	−42	29	13	3.02	
		L Superior frontal gyrus	09	−15	44	31	3.67	
		L Superior frontal gyrus	10	−24	56	13	3.50	
	2	R Insula	13	45	−7	13	2.09	1537
		R Lentiform nucleus		27	−1	16	2.62	
	3	L/R RSC	30	0	−49	13	3.93	7045
		L RSC	29	−9	−43	16	3.31	
		L dPCC	31	−9	−55	19	3.47	
	4	R dPCC	23	3	−28	28	2.82	1591
		L dPCC	23	−6	−19	31	2.35	
	5	L Thalamus		−18	−22	7	2.63	3801
		L Parahippocampal gyrus		−24	−16	−14	3.16	
	6	L Superior temporal gyrus	41	−54	−25	10	2.66	1476
		L Postcentral gyrus	43	−57	−13	16	2.74	
Tdys > Gdys	1	L Superior frontal gyrus	09	−15	50	25	2.81	2918

Tdys = tinnitus-related sentences; Neu = neutral sentences; Gdys = generally negative sentences; R = right; L = left; pACC = perigenual anterior cingulate cortex; sACC = subgenual anterior cingulate cortex; aMCC = anterior midcingulate cortex; RSC = retrosplenial cortex; dPCC = dorsal posterior cingulate cortex; BA = Brodman area.

connectivity analysis when highly and low distressed tinnitus patients were compared, but did not correlate with tinnitus-related distress however. Despite a contribution of the scACC, we found a correlation with distress of the pACC and aMCC.

4.1. The role of frontal regions in tinnitus-related distress

Activity in the left middle frontal gyrus (BA 6) differentiated highly and low distressed tinnitus patients. A difference in BOLD fMRI signal of the left middle frontal gyrus was also found when highly distressed tinnitus patients were compared to healthy controls. Within the group of highly distressed tinnitus patients a higher activation of the left middle frontal gyrus was demonstrated when the reading of tinnitus-related sentences was contrasted with the reading of neutral sentences, but also in comparison to the reading of generally negative sentences. Furthermore, the activity in the left middle frontal gyrus correlated with tinnitus-related distress.

The middle frontal gyrus has been linked to the perception of tinnitus (Weisz et al., 2005; Mirz et al., 1999) and recently to tinnitus distress (De Ridder, 2011). Jastreboff suggested the prefrontal cortex as a possible region for integrating sensory and emotional characteristics of tinnitus (Jastreboff, 1990). Since we compared highly and low distressed tinnitus patients and due to the fact that our groups did not differ in tinnitus loudness, our results seem to stress the role of the prefrontal cortex in the emotional processing of tinnitus. However, in contrast to the above mentioned studies we used verbal material in our study.

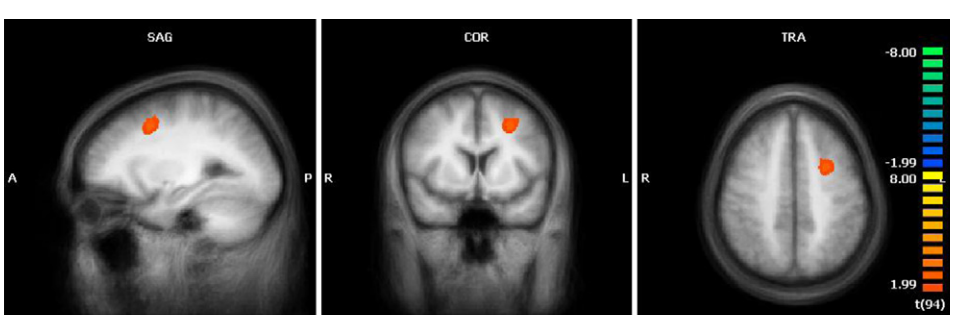

Fig. 6. It shows the cluster in which highly distressed tinnitus patients respond stronger to tinnitus-related sentences compared to neutral sentences in comparison to low distressed tinnitus patients. Cluster level threshold is 44 with $p < 0.05$ and the peak voxel is located at $x = -27$, $y = 8$, $z = 43$ in the left middle frontal gyrus.

Table 5
Peak voxels and corresponding brain regions of the connectivity analysis with the seed region in the left middle frontal gyrus.

Cluster	Region	BA	Peak voxel			*t*-value	Cluster size (mm^3)
			x	*y*	*z*		
HDT							
1	R Supramarginal gyrus	40	51	−55	31	4.93	2327
	R Inferior parietal lobule	40	42	−55	37	4.28	
2	L/R pACC	32	0	41	13	3.79	104405
	L aMCC	24	−9	26	16	4.13	
	L aMCC	32	−21	11	37	18.71	
	L pMCC	24	−27	−19	34	6.05	
	L Inferior frontal gyrus	46	−36	35	10	4.47	
	L Insula	13	−39	14	16	7.32	
	L/R Medial frontal gyrus	09	0	38	25	6.22	
	L Medial frontal gyrus	08	−9	20	49	12.07	
	L Medial frontal gyrus	06	−15	−19	52	3.16	
	L Middle frontal gyrus	06	−21	11	61	3.25	
	L Middle frontal gyrus	09	−30	17	28	8.65	
	L Middle frontal gyrus	46	−42	26	22	5.75	
	L Middle temporal gyrus	39	−51	−67	28	7.91	
	L Postcentral gyrus	02	−48	−31	34	4.59	
	L Precentral gyrus	04	−33	−13	46	4.01	
	L Precentral gyrus	09	−36	5	40	12.44	
	L Precentral gyrus	06	−48	−10	25	4.21	
	L Superior frontal gyrus	08	−18	26	46	12.06	
	L Superior frontal gyrus	10	−24	44	19	4.03	
	L Superior frontal gyrus	06	−24	14	49	10.80	
	L Superior temporal gyrus	39	−39	−49	25	7.20	
	L Superior Temporal Gyrus	22	−57	−49	19	4.71	
	L Supramarginal gyrus	40	−45	−43	37	5.72	
	R Medial frontal gyrus	09	3	50	25	6.28	
	R Medial frontal gyrus	08	3	23	43	7.54	
	R Middle frontal gyrus	46	42	20	25	3.08	
	R Middle frontal gyrus	06	30	8	46	4.95	
	R Paracentral lobule	06	3	−28	55	4.62	
	R Precentral gyrus	09	33	11	34	7.05	
	R Superior frontal gyrus	08	18	20	46	6.32	
3	L Precuneus	07	−3	−55	31	5.82	6542
	L RSC	30	−6	−49	19	7.28	
	L Caudate		−18	−34	25	4.18	
4	L Middle frontal gyrus	11	−39	47	−14	3.30	3139
HDT vs. LDT							
1	R Medial frontal gyrus	09	3	47	22	4.72	1497
2	R vPCC	23	4	−49	25	2.80	888
	L RSC	30	−9	−43	22	3.97	
3	L Insula	13	−39	20	1	3.53	428
4	L Precentral gyrus	06	−48	−10	26	4.25	984
	L Postcentral gyrus	02	−48	−22	28	3.47	
5	L Superior temporal gyrus	39	−42	−55	28	2.84	202
	L Middle temporal gyrus	39	−51	−61	28	3.09	

HDT = highly distressed tinnitus patients, LDT = low distressed tinnitus patients; R = right; L = left; BA = Brodman area; pACC = perigenual anterior cingulate cortex; aMCC = anterior midcingulate cortex, pMCC = posterior midcingulate cortex; RSC = retrosplenial cortex; vPCC = ventral posterior cingulate cortex.

The reading of emotional compared to neutral words has also been linked to the left middle frontal gyrus (Hirata et al., 2007). So, this region also seems to be connected to the processing of language-related emotional content. Furthermore this region was found to be activated in a study done by Dolcos et al. (2004), in which remembered arousing emotional and neutral pictures were compared to non-remembered pictures. The left middle frontal gyrus (BA 6/9) showed a higher activation for arousing

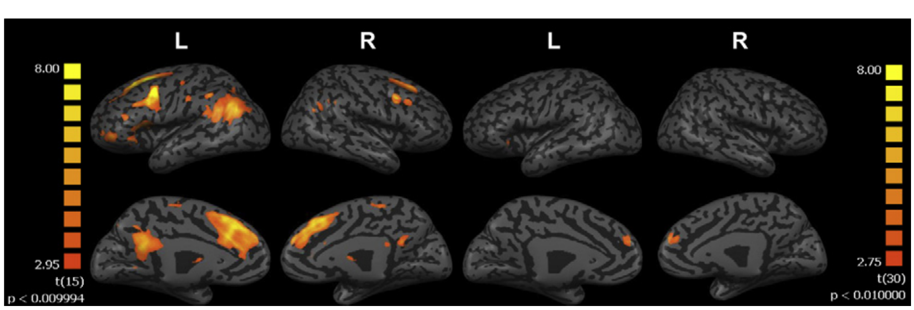

Fig. 7. Connectivity analysis with the seed region in the left middle frontal gyrus for HDT (left) and HDT compared to LDT (right).

Table 6
Correlations with tinnitus-related distress.

Contrast	Cluster	Region	BA	*r*	Peak voxel			Cluster size (mm³)
					x	*y*	*z*	
Tdys > Neu	1	R Inferior frontal gyrus	46	0.59	57	29	10	5153
		R Inferior frontal gyrus	09	0.61	42	14	22	
		R Middle frontal gyrus	09	0.61	45	23	31	
		R Superior frontal gyrus	09	0.51	42	35	25	
	2	R Middle frontal gyrus	06	0.57	51	11	46	591
	3	R Inferior parietal lobule	07	0.58	42	−67	49	403
		R Inferior parietal lobule	40	0.53	39	−58	43	
	4	R Claustrum		0.56	27	20	1	1701
	5	R Superior frontal gyrus	09	0.59	30	50	28	1109
	6	R aMCC	24	0.57	21	5	43	20568
		R aMCC	32	0.66	15	17	34	
		L aMCC	24	0.61	−9	11	28	
		R Medial frontal gyrus	06	0.58	6	29	37	
		L Medial frontal gyrus	06	0.60	−12	−1	52	
		L Middle frontal gyrus	06	0.68	−24	5	46	
		L Middle frontal gyrus	09	0.64	−33	29	28	
		L Superior frontal gyrus	08	0.55	−24	35	49	
	7	R Superior frontal gyrus	09	0.64	6	56	25	1066
	8	L Claustrum		0.68	−30	17	−2	1705
		L Insula	13	0.49	−39	11	4	
	9	L Supramarginal gyrus	40	0.54	−36	−46	34	545
Tdys > Gdys	1	R Inferior parietal lobule	40	0.56	45	−52	52	499
	2	R Superior parietal lobule	07	0.55	18	−64	55	587
	3	R Middle frontal gyrus	06	0.49	24	−4	46	298
	4	R Superior frontal gyrus	09	0.67	9	50	25	1167
	5	R aMCC	32	0.54	9	14	34	800
		L aMCC	32	0.58	−9	23	28	
	6	L Medial frontal gyrus	08	0.57	−9	26	40	274
	7	L pACC	24	0.51	−12	2	40	290
	8	L Lingual gyrus		0.53	−18	−76	4	359
	9	L Uncus	34	−0.54	−18	−7	−20	561
		L Uncus	28	−0.50	−30	2	−20	
	10	L Superior temporal gyrus	38	−0.53	−33	17	−32	538
	11	L Inferior parietal lobule	40	0.56	−48	−49	37	272
	12	L Inferior parietal lobule	40	0.66	−66	−37	22	333

Tdys = tinnitus-related sentences; Neu = neutral sentences; Gdys = generally negative sentences; BA = Brodman area; *r* = correlation coefficient; aMCC = anterior mid-cingulate cortex; pACC = perigenual anterior cingulate cortex.

emotional (negative and positive) compared to non-emotional, non-arousing (neutral) material. Thus, arousing material seems to be processed in working memory more intensively, therefore leading to an improved retention (Dolcos et al., 2004). Activations of the middle frontal gyrus could also be shown in depressed individuals during rumination (Cooney et al., 2010). In our study, tinnitus-related sentences were supposed to be instances of negative cognitions about tinnitus. Furthermore, the tinnitus-related sentences were rated more negative and arousing in comparison to neutral sentences. Thus, similar to rumination, our findings give rise to the assumption that the left middle frontal gyrus plays a role in the maintenance of dysfunctional cognitions in working memory.

We identified several other frontal brain regions that correlated positively with tinnitus-related distress. However most of these regions are part of the DLPFC (BA 9, 46). In the Global Brain Model (Schlee et al., 2011) the DLPFC is seen as a key structure and considered as a main structure responsible for the top-down influence on the auditory cortex. According to the model, the DLPFC enhances the excitability of the temporal cortices. The extent of this influence is supposed to be mediated by the amount of perceived distress. Other studies support this view. The DLPFC has been linked to auditory attention (Voisin et al., 2006) and the top-down modulation of auditory processing (Mitchell et al., 2005). Our study, however, stresses the role of the right medial frontal cortex in tinnitus-related distresses. Correlations with parts of the right medial frontal cortex were found in the connectivity analysis in the highly distressed tinnitus group. Those correlations were higher for highly distressed tinnitus patients compared to low distressed tinnitus patients and activity in the right medial frontal cortex correlated with subjective tinnitus distress.

4.2. The involvement of the limbic system in tinnitus distress

Limbic structures that were identified in other studies of tinnitus seem to be the ACC, PCC, insula and the parahippocampal gyrus (Plewnia et al., 2007; Vanneste et al., 2010b; De Ridder et al., 2011). We found significant positive correlations between the TQ scores and BOLD fMRI signal in the left insula, left pACC and bilaterally in the aMCC. BOLD signal in the left insula, the pACC and left aMCC also correlated with the signal in the seed region in the connectivity analysis. Thus, stressing their role in the distress network. The aMCC had not been linked to tinnitus distress, yet. However, a functional MCC circuit was suggested by Vogt et al. (2003), in which the aMCC should be associated with fear, fear associated memories and cognitive schemata. A recent coordinate based (voxel-by-voxel) meta-analysis over 192 studies, in which negative emotions were induced (fear, anger, disgust), painful stimuli delivered (e.g. heat, electric shock) or tasks used that required cognitive control (Stroop tasks, Go/No-Go-tasks and Eriksen Flanker tasks) revealed that negative affect, pain and cognitive control activated a cluster in the dorsal portion of aMCC (Shackman et al., 2011). Hence, in our study the correlation of aMCC-activity with tinnitus distress might reflect negative emotions due to the tinnitus-related sentences. The pACC has been linked to the perceived unpleasantness of observed noxious or disgusting stimuli (Benuzzi et al., 2008). Since we did not find differences in valence between the groups, pACC activity might be modulated by the relevance of the tinnitus-related sentences.

While the aMCC and the pACC seem to be involved in the emotional processing of tinnitus-related cognitions, it has been reported that the insula is involved in the regulation of the autonomic nervous system (Nagai et al., 2010), which, according to Jastreboff (Jastreboff et al., 1996), is responsible for the sensation of distress. It has been shown that a change in regional cerebral blood flow in the left insula, induced by a mental arithmetic task, correlated positively with subjective ratings of stress (Wang et al., 2005). Furthermore the insula is associated with interoceptive attention (Pollatos et al., 2007). Thus, in accordance with other studies we identified the pACC and insula to be involved in tinnitus annoyance. We failed to find a correlation with activity of the parahippocampal gyrus, though highly distressed tinnitus patients showed a higher activation in the parahippocampal gyrus in comparison to healthy controls. In addition to other studies we identified an association of the aMCC with tinnitus-related distress.

4.3. The role of the precuneus in tinnitus annoyance

In addition we assumed the precuneus to be involved in tinnitus-related distress. In accordance with our assumption, the connectivity analysis of the highly distressed tinnitus patients suggested the precuneus to be involved in the distress network of chronic tinnitus. However, the precuneus did not correlate higher with the seed region in comparison to the low distressed tinnitus patients. In addition there was no correlation of the precuneus with the TQ. Though highly distressed tinnitus patients showed a precuneus activation in response to tinnitus-related sentences compared to the other two stimuli conditions, they failed to show any precuneus activation when compared to low distressed tinnitus patients and healthy controls. This finding is inconclusive with regard to the assumptions of the Global Brain Model, that suggests the precuneus to be a key component in the distress network. However, this difference may be due to a lack of power, since we can show a correlation of activity in the left precuneus and tinnitus distress at an uncorrected cluster threshold of $p = .02$.

4.4. An aspecific distress network

The further question that needs to be addressed is whether those brain areas that are involved in tinnitus distress are specific for tinnitus-related distress. Recently, De Ridder (2011) proposed an aspecific network consisting of the amygdala, the ACC and the anterior insula as being responsible for tinnitus-related distress. Indeed, a number of the above mentioned brain areas are involved, not only in tinnitus, but also in other conditions eliciting psychological distress. It has been shown that threatening bodily sensations, such as pain and dyspnea, activate the left and right insula, left dACC, right medial thalamus and left amygdala (von Leupoldt et al., 2009). Pictures with scenes of social rejection compared to scenes of acceptance activate the middle frontal gyri, dACC, PCC, parahippocampal gyri, left precentral gyrus and right medial and inferior frontal gyrus (Kross et al., 2007). Subjectively electrosensitive patients showing a high rate of medically unexplained symptoms activated the insulae, inferior, middle and superior frontal gyri and ACC in reaction to sham mobile phone exposure with a dummy mobile phone, which was supposed to work under MRI-conditions compared to, also unpleasant, heat stimuli (Landgrebe et al., 2008). According to these studies and our own findings, the idea of an aspecific distress network is supported.

4.5. Implication for neuromodulatory approaches

What are practical implications of our findings? As mentioned before, an understanding of the distress network could help to identify target regions for neuromodulatory approaches. Recently, several studies examined the effect of TMS on tinnitus (Plewnia et al., 2007; Kleinjung et al., 2008; Kreuzer et al., 2011). Another method applied to the treatment of tinnitus is transcranial direct current stimulation (tDCS). A group of 543 tinnitus patients received tDCS with the anode placed over the right DLPFC and the cathode placed on the left DLPFC. Of this group, 134 participants responded to the treatment with a reduction in tinnitus intensity of 28% and a reduction of tinnitus distress of 31% (Vanneste et al., 2010a). However, 70% of the participants did not respond to the treatment. Thus, the ideal stimulation site is yet to be found. We identified two brain regions which might be candidates for neuromodulatory approaches; the left middle frontal gyrus and the right medial frontal gyrus. The left middle frontal gyrus is a candidate since its activation differed between highly and low distressed tinnitus patients. The right medial frontal gyrus was identified in the connectivity analysis and additionally correlated with tinnitus-related distress. We suggest those areas as stimulation sides for a reduction of tinnitus-related distress.

4.6. Limitations of the study

There are some limitations of the study. Some issues directly concern the use of fMRI. FMRI is a correlative technique that uses an indirect measure of brain activity (Buckner and Logan, 2001; see Logothetis, 2008 for details). Therefore it would be eligible for future studies to combine fMRI with other techniques, such as EEG. Another issue concerns fMRI as a method in tinnitus research; the noise produced by the MRI (Danesh et al., 2003; Lockwood et al., 2004). The noise of the MRI could mask the tinnitus of the participants (Danesh et al., 2003). Additionally, it has been shown that scanner-noise can have differential effects even on non-auditory brain areas as a function of the cognitive demand of tasks (Tomasi et al., 2005). However, since our study aimed to investigate the processing of tinnitus-related verbal material, it was not necessary to perceive the tinnitus during the task. Furthermore, the task did not vary over the different stimuli conditions. Thus, differential effects of the scanner-noise seem unlikely.

Other possible limitations of the study might be the distress levels of our participants, the stimuli selection or differences in vocabulary. The high distress group included mostly participants with a tinnitus severity grade of two in the TQ which accounts for a moderate level of distress and no participants were graded four. A stronger discrimination between the high and low distress group might have been beneficial, since we did not find activations of the precuneus and limbic brain regions between highly and low distressed participants when we compared tinnitus-related sentences to neutral sentences and no differences in comparison to generally negative sentences. This view is supported by the comparison of highly distressed tinnitus patients with healthy controls, where we found activations in several frontal and limbic areas when we compared the reading of tinnitus-related sentences to the reading of neutral sentences. However, patients with a moderate tinnitus severity take often part in therapy studies that aim to reduce distress (Kröner-Herwig et al., 2003; Zachriat and Kröner-Herwig, 2004; Rief et al., 2005). This indicates that patients with a moderate level of tinnitus distress seek help. Still we cannot rule out that the sample selection is a limiting factor. Another possible explanation, however, might be the stimuli selection. We found no differences in valence and arousal of tinnitus-related sentences and generally negative sentences between the groups. Furthermore we did not find differences between highly and low distressed patients in the comparison of tinnitus-related sentences with generally negative sentences and only one region was more activated when highly distressed tinnitus patients were compared with healthy controls. Therefore future studies should explore the individual cognitions about tinnitus, since those cognitions are most likely to be negative and relevant for the patients. Thus, we recommend the use of idiosyncratic stimulus material.

Another issue could be the difference of the two tinnitus groups in their vocabulary test scores. It might be that some of the differences in neural activity between highly and low distressed tinnitus patients were due to novelty of words. In an fMRI-study that addressed effects of word novelty, participants learned a list of 10 words before the scanning procedure (familiar words). In an event-related design familiar and novel words were presented. Novel words were found to activate the anterior left hippocampal region (Saykin et al., 1999). Since this region was not activated when we compared highly and low distressed tinnitus patients, it seems unlikely that the differences between tinnitus groups are due to novelty of words.

5. Conclusions

We hypothesized a higher activity of the precuneus, frontal and limbic areas in highly distressed tinnitus patients compared to low distressed tinnitus patients and healthy controls and positive correlations of those areas with tinnitus-related distress. We found differences in limbic and frontal areas in highly distressed tinnitus patients in comparison to healthy controls and a higher activation of the left middle frontal gyrus in comparison to low distressed tinnitus patients. A connectivity analysis performed on this cluster revealed connections to limbic areas; pACC, MCC, RSC and insula, frontal areas and the precuneus. The activity in several brain regions including the DLPFC, the medial, middle and superior frontal gyrus, aMCC, pACC and insula correlated positively with tinnitus-related distress. Those hypothesized regions that appeared in the connectivity analysis and in addition correlated with tinnitus-related distress are assumed to be most likely part of the distress network. Those regions are the left pACC, left insula, left aMCC, DLPFC, left superior frontal gyrus and bilaterally medial and middle frontal gyrus. Thus, our hypotheses were largely confirmed. We presume an aspecific distress network, not unique to tinnitus. The right medial frontal gyrus and left middle frontal gyrus are suggested as target regions for neuromodulatory approaches. For future studies, it would be interesting to use individual dysfunctional cognitions of tinnitus patients as stimulus material and examine the neural activations elicited by those stimuli and how those activations change after a distress reducing cognitive-behavioral therapy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.heares.2012.03.003.

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Supplementary Material

List of the stimulus material

Tinnitus-Related Sentences	
Ich denke, man sollte junge Leute vor Discobesuchen warnen.	*I think, one should warn young people to go to a club.*
Manchmal frage ich mich, ob ich einen Hirntumor habe.	*Sometimes I wonder if I have a brain tumor.*
Ich frage mich öfters, warum das Ohrgeräusch denn gerade mich getroffen hat.	*Often, I ask myself, why it had to be me having tinnitus.*
Das Ohrgeräusch ist wohl das erste Zeichen dafür, dass mein Körper langsam nachlässt.	*The tinnitus is probably the first sign that my bodily condition slowly worsens.*
Ich muss mich entscheiden zwischen Teilnahme am Leben und Sorge um mein Gehör.	*I have to decide between taking part in a normal life and to worry about my sense of hearing.*
Wird das Ohrgeräusch schlimmer, suche ich die Ursache.	*When the tinnitus worsens, I am looking for a cause.*
Wenn mein Ohrgeräusch plötzlich schlimmer wird, kann es auf Dauer schlechter werden.	*When my tinnitus suddenly worsens, it could stay that way.*
Ich frage mich, wie schlimm so ein Ohrgeräusch noch werden kann.	*I wonder how bad that tinnitus can get.*
Ich rate anderen, regelmäßig zum Ohrenarzt zu gehen.	*I advise others to regularly see the otolaryngologist.*
Ich werde das Ohrgeräusch niemals los.	*I will never get rid of the tinnitus.*
Wird mein Ohrgeräusch noch schlimmer, dann wird es mein Gehör schädigen.	*If my tinnitus worsens even more, it will damage my sense of hearing.*
Vor meinem Ohrgeräusch war alles in Ordnung und jetzt ist alles furchtbar.	*Before my tinnitus everything was good, now everything is horrible.*
Innerlich gehe ich davon aus, dass sich mein Ohrgeräusch sicher weiter verschlimmern wird.	*Deep down, I believe that my tinnitus will get worse.*
Eine Erkältung zu riskieren kann ich mir nicht leisten, sie könnte sich auf meine Ohren auswirken.	*I cannot risk a cold, it could influence my hearing.*
Hat man gesunde Ohren, hat man auch nie, wie ich, Ohrgeräusche.	*If one has healthy ears, one does not have tinnitus, like I do.*
Generally Negative Sentences	
Ich denke recht oft, dass ich ein Versager bin.	*Often, I think I am a loser.*
Es enttäuscht mich immer, wenn mich jemand nicht mag.	*I am disappointed, when someone does not like me.*
Wenn ich meine Probleme nicht lösen kann, fühle ich mich als Versager.	*I feel like a loser, if I cannot solve my problems.*
Mir ist es peinlich, wenn ich in der Gegenwart anderer einen Fehler mache.	*I am embarrassed, when I do something wrong in front of others.*
Ich kann es einfach nicht ertragen, andere Leute um einen Gefallen zu bitten.	*I cannot endure to ask others for help.*
Manchmal habe ich das Gefühl, ich sei wertlos.	*Sometimes I feel worthless.*
Ich fühle mich äußerst unwohl, wenn Dinge nicht an ihrem Platz sind.	*I feel really uncomfortable, when things are out of its place.*
Es gibt Zeiten, in denen kann ich mich einfach nicht ausstehen.	*There are times, where I cannot stand myself.*
Wenn mich Leute nicht mögen, bin ich wertlos.	*If people do not like me, I am worthless.*
Ich habe häufig Mitleid mit mir.	*Often, I feel sorry for myself.*
Ich glaube, dass ich mein Leben nicht richtig im Griff habe.	*I do not think that I have my life under control.*
Ich kann es nicht aushalten, wenn Leute nicht billigen, was ich tue.	*I cannot bear it, when people do not approve what I am doing.*
Ich ertrage es einfach nicht, wenn andere Leute nicht mögen, was ich tue.	*I cannot bear it, when people do not like what I am doing.*
Ich vermeide es lieber, Dinge auszuprobieren, wenn ich mir über das Ergebnis nicht ziemlich sicher bin.	*I avoid trying new things, if I am not pretty sure about the outcome.*
Mir ist es recht unangenehm, wenn ich mal unpassend gekleidet bin.	*I feel pretty uncomfortable, if I am not dressed the right way.*

Neutral Sentences	
Wenn ich Mittag esse, benutze ich stets eine Gabel.	*I use a fork for lunch.*
Zum Bügeln meiner Wäsche benutze ich immer ein Bügeleisen.	*I use an iron to iron my clothes.*
Um einen Nageln in die Wand zu schlagen, verwende ich einen Hammer.	*I use a hammer to put a nail into the wall.*
Damit meine Wohnung nicht dreckig wird, trage ich bei mir zu Hause Hausschuhe.	*At home I wear slippers, to prevent my flat from getting dirty.*
Wenn ich mal Eintopf oder Suppe zubereite, verwende ich dazu einen großen Kochtopf.	*When I prepare soup or stew, I use a big cooking pot.*
Um etwas zu zimmern, verwende ich ein Brett.	*To timber something, I use a board.*
Wenn es in meinem Wohnzimmer kalt ist, dann schließe ich die Tür.	*When it is cold in my living room, I close the door.*
Getränke wie Wasser oder Saft, trinke ich immer aus einem Becher.	*I use a cup to drink beverages like water or juice.*
Zum Schreiben eines Briefes verwende ich blaue Tinte.	*I use blue ink to write a letter.*
Ich schaue regelmäßig auf meine Uhr.	*Regularly, I look at my watch.*
Um Zeichnungen von etwas zu machen, verwende ich immer einen Bleistift.	*I use a pencil to draw something.*
Um etwas an die Wand zu hängen, benutze ich meistens einen Nagel.	*I use a nail to put something up the wall.*
Wenn ich bei mir daheim am Schreibtisch arbeite, sitze ich auf einem Stuhl.	*When I work at home at my desk, I sit on a chair.*
Wenn ich etwas Neues für meine Wohnung brauche, gehe ich in ein Einrichtungshaus und kaufe Möbel.	*If I need something new for my flat, I go to a shop and buy furniture.*
Um zu meiner Arbeit zu gelangen, benutze ich immer mein Auto.	*I always use my car to get to work.*

Questionnaire of dysfunctional beliefs about tinnitus (Hiller, 1999, unpublished)

Wenn ich das Gefühl habe, dass sich an meinen Ohren oder meinem Gehör etwas verändert, beunruhigt mich das sofort.	*When I am feeling that something in my hearing or my ears changes, I am worried instantly.*
Wenn mein Ohrgeräusch nicht durch Medikamente zu behandeln ist, muss es sich um einen schweren Fall handeln.	*If my tinnitus cannot be treated with drugs, it must be a tough case.*
Es ist möglich, mit absoluter Sicherheit zu wissen, ob hinter dem Ohrgeräusch eine ernsthafte Erkrankung steckt oder nicht.	*It is possible to say without doubt whether the tinnitus is a symptom of a severe medical condition.*
Plötzliche Verschlimmerungen des Ohrgeräusches können eine dauerhafte Verschlechterung ankündigen.	*A sudden worsening of the tinnitus could predict a permanent change.*
Entweder ich oder mein Arzt müssen in der Lage sein, für mein Ohrgeräusch und die damit zusammenhängenden Symptome Erklärungen zu finden.	*Either me or my doctor must be able to find answers form my tinnitus and the associated symptoms.*
Manchmal macht das Ohrgeräusch mich wahnsinnig, dann denke ich darüber nach, ob ich einen Hirntumor (Geschwulst im Kopf) habe.	*Sometimes the tinnitus makes me crazy and I wonder, if I have a brain tumor (lump inside the head).*
Das Ohrgeräusch wird mich noch verrückt machen.	*The tinnitus is going to make me crazy.*
Als Betroffener sollte man regelmäßig zum Ohrenarzt gehen, um der Verschlechterung der Ohrgeräusche vorzubeugen.	*As tinnitus patient, one should go to the doctors regularly to prevent worsening of the condition.*
Ich bin immer darum bemüht, so zu leben, dass sich mein Ohrgeräusch möglichst nicht verschlechtern kann.	*I am exerted to live in a way that does not worsen my tinnitus.*
Lärm muss ich vermeiden, um mein Gehör zu schonen.	*I must avoid noise to preserve my hearing.*
Wenn ich nicht ständig auf meine Ohren und mein Gehör achte, könnte sich unbemerkt eine Verschlechterung einstellen.	*If I am not always focused on my ears, a worsening could not be noticed.*
Ich bin über Ohrgeräusche und alles, was damit zusammenhängt, gut informiert, um bei mir selbst nichts zu übersehen.	*I am well informed about tinnitus and everything that is related to it, so I do not miss something with regard to myself.*
Ich frage mich öfters, warum es mit dem Ohrgeräusch ausgerechnet mich getroffen hat.	*Often, I ask myself, why it had to be me having tinnitus.*
Das Ohrgeräusch ist wohl das erste Anzeichen dafür, dass mein Körper langsam nachlässt.	*The tinnitus is probably the first sign that my bodily condition slowly worsens.*
Ich hätte mein Ohrgeräusch verhindern können, wenn ich vorher regelmäßig zum Ohrenarzt gegangen wäre.	*I could have prevented my tinnitus, if I had gone to the Otolaryngologist regularly.*
Wenn man gesunde Ohren hat, hat man auch nie Ohrgeräusche.	*If one has healthy ears, one does not have tinnitus.*
Wenn das Ohrgeräusch schlimmer wird, frage ich mich die ganze Zeit, woher das kommt.	*When the tinnitus worsens, I cannot stop wondering about the cause.*
Wegen des Ohrgeräuschs muss ich mehr darauf achten, mich möglichst keinen Umweltgiften auszusetzten.	*Because of the tinnitus, I have to pay more attention not to expose myself to environmental pollutants.*
Das Ohrgeräusch bedeutet, dass ich ein hohes Risiko für einen Schlaganfall habe.	*The tinnitus means that I have a high risk for stroke.*
Solange ich unter diesem Ohrgeräusch leide, werde ich mich nie mehr so konzentrieren können wie früher.	*As long as I suffer from tinnitus, I will not be able to concentrate as good as I used to.*
Ich glaube, dass mein Ohrgeräusch durch elektronische oder elektromagnetische Strahlung (z.B. Handy, Computer, Elektrokabel…) verursacht wurde.	*I believe my tinnitus was caused by electric or electromagnetic waves (e.g. mobile phones, computer, electric cables…).*
Ich würde anderen, die noch kein Ohrgeräusch haben, raten, sich regelmäßig eingehend vom Ohrenarzt untersuchen zu lassen.	*I would advise others who do not have tinnitus yet to regularly see the otolaryngologist for a detailed examination.*
Ich muss einen Weg finden, um einmal wieder völlige	*I have to find a way to experience total silence again.*

Stille um mich zu haben.	
Manchmal frage ich mich, wie schlimm denn so ein Ohrgeräusch noch werden kann.	*Sometimes, I wonder how bad that tinnitus can get.*
Leider muss ich mich entscheiden zwischen der Teilnahme am normalen Leben und der Sorge um mein Gehör.	*Unfortunately, I have to decide between taking part in a normal life and to worry about my sense of hearing.*
Mein Ohrgeräusch ist ein Anzeichen dafür, dass ich eventuell einen Herzinfarkt bekommen könnte.	*My tinnitus is a sign of a potential heart attack.*
Wenn mein Ohrgeräusch morgens schon schlimm ist, weiß ich, dass es kein guter Tag werden kann.	*If my tinnitus is already bad in the morning, I know it won't be a good day.*
Man sollte junge Leute dringend vor Discobesuchen warnen, damit sie nicht unnötig ein Ohrgeräusch riskieren.	*I think, one should urgently warn young people to go to a club, so they do not risk a tinnitus.*
Innerlich gehe ich davon aus, dass sich mein Ohrgeräusch sicherlich weiter verschlimmern wird.	*Deep down, I believe that my tinnitus will get worse.*
Ich bin mir so gut wie sicher, dass ich das Ohrgeräusch nie wieder loswerde.	*I am convinced that I will never get rid of the tinnitus.*
Wenn mein Ohrgeräusch noch schlimmer wird, dann wird es mein Gehör schädigen.	*If my tinnitus worsens even more, it will damage my sense of hearing.*
Vor dem Ohrgeräusch war alles in Ordnung – jetzt ist alles furchtbar.	*Before my tinnitus everything was good, now everything is horrible.*
Eine Erkältung zu riskieren, kann ich mir nicht leisten, da sie sich auf meine Ohren auswirken könnte.	*I cannot risk a cold, it could influence my hearing.*

Results of the contrast Gdys>Neu.

Contrast	Cluster	Region	BA	Peak Voxel			t-value	Cluster Size (mm²)
HDT>HC	1	L/R vPCC	23	0	-52	16	2.51	1006
	1	L Precuneus	31	-9	-58	19	2.37	
HDT>LDT	1	R Medial Frontal Gyrus	10	9	56	16	2.58	1458
	1	L Medial Frontal Gyrus	10	-9	56	3	2.48	
	1	R pACC	32	3	47	7	2.15	

Tdys= tinnitus-related sentences; Neu= neutral sentences; Gdys= generally negative sentences; R= right; L= left; BA= Brodman area; pACC= perigenual anterior cingulate cortex; aMCC= anterior midcingulate cortex; RSC= retrosplenial cortex; dPCC= dorsal posterior cingulate cortex; vPCC= ventral posterior cingulate cortex.

Peak voxels of the within group results of HDT.

Contrast	Cluster	Region	BA	Peak Voxel			t-value	Cluster Size (mm^3)
				x	y	z		
Tdys>Neu	1	R Middle Temporal Gyrus	21	54	-4	-14	4.18	6072
		R Superior Temporal Gyrus	38	48	14	-20	3.79	
		R Superior Temporal Gyrus	41	45	-37	10	3.32	
	2	R Inferior Frontal Gyrus	47	42	20	-5	3.67	701
	3	R Declive		24	-61	-14	4.19	1162
	4	R Medial Frontal Gyrus	10	9	44	10	3.59	7253
		R Superior Frontal Gyrus	09	6	56	25	4.35	
	5	R Cuneus	19	15	-82	32	3.13	21165
		R RSC	29	3	-46	16	4.51	
		R Precuneus	31	12	-70	28	4.32	
		L Precuneus	31	-6	-64	22	7.25	
	6	L dPCC	23	-3	-22	28	4.77	1683
	7	L Declive		-24	-64	-17	3.44	3204
		L Fusiform Gyrus	19	-21	-58	-8	3.78	
		L Lingual Gyrus	18	-15	-67	1	3.77	
	8	L Medial Frontal Gyrus	09	-12	41	19	3.41	5364
		L Superior Frontal Gyrus	09	-18	47	28	5.23	
		L Superior Frontal Gyrus	10	-24	56	13	2.90	
	9	L Parahippocampal Gyrus	36	-30	-28	-17	-5.21	1207
	10	L Lingual Gyrus		-27	-73	4	3.35	469
		L Lingual Gyrus	18	-33	-73	-5	2.69	
	11	L Superior Temporal Gyrus	38	-48	5	-14	6.52	10633
	12	L Middle Frontal Gyrus	06	-36	2	46	3.23	487
	13	L Middle Temporal Gyrus	21	-60	-49	8	3.21	5084
		L Superior Temporal Gyrus	41	-45	-37	10	2.91	
		L Supramarginal Gyrus	40	-48	-49	19	5.35	
Tdys>Gdys	1	R Angular Gyrus	39	30	-61	37	3.41	2622
		R Middle Temporal Gyrus	39	42	-55	25	2.96	
	2	R Thalamus		18	-31	10	-3.69	641
	3	R Declive		24	-58	-14	3.83	994
		R Lingual Gyrus	19	15	-61	-5	3.00	
	4	R Precuneus	31	18	-70	28	2.96	991
		L Precuneus	31	-3	-67	25	3.11	
	5	R Superior Frontal Gyrus	09	15	44	31	3.65	844
	6	R RSC	29	3	-43	10	3.34	481
	7	L dPCC	23	-3	-34	28	3.76	1834
		L/R Precuneus	31	0	-49	34	2.75	
	8	L Declive		-21	-61	-11	3.53	2052
		L Lingual Gyrus	18	-15	-67	1	4.13	
	9	L Superior Frontal Gyrus	09	-18	47	28	3.50	513
	10	L Caudate		-21	-40	19	-2.93	933
		L Insula	13	-30	-31	19	-3.62	
	11	L Inferior Frontal Gyrus	09	-42	14	22	3.14	4413
		L Middle Frontal Gyrus	06	-33	11	47	4.18	
	12	L Inferior Parietal Lobule	40	-51	-46	22	4.95	13396
		L Middle Temporal Gyrus	21	-48	-7	-14	3.65	
		L Middle Temporal Gyrus	22	-60	-43	4	3.81	
		L Precuneus	07	-24	-67	37	3.11	
		L Superior Temporal Gyrus	39	-36	-58	31	4.16	
		L Superior Temporal Gyrus	22	-66	-37	20	4.38	
Gdys>Neu	1	R Superior Temporal Gyrus	42	63	-31	13	3.39	528
	2	R Middle Temporal Gyrus	39	39	-58	22	-4.57	4220
	3	R Lentiform Nucleus		33	-25	1	3.64	1469
	4	R Claustrum		36	5	-2	3.73	575
	5	R Claustrum		27	-4	19	3.67	569
	6	R aMCC	33	9	23	16	3.94	1997
		L/R pACC		0	29	4	3.48	

	L Caudate		-12	26	4	3.05	
7	R Medial Frontal Gyrus	09	9	41	16	3.84	1871
8	R Thalamus		6	-16	19	3.41	1445
	L dPCC	23	-3	-19	28	4.14	
9	L/R vPCC	23	0	-52	22	3.64	3974
	L Precuneus	31	-6	-64	22	4.53	
10	L RSC	29	-9	-43	7	-3.72	597
11	L Middle Frontal Gyrus	06	-27	15	46	-4.10	1566
12	L Middle Temporal Gyrus	39	-30	-61	28	-4.88	7606
	L Middle Temporal Gyrus	19	-36	-58	13	-3.81	
13	L Middle Frontal Gyrus	09	-39	17	31	-3.71	1642
	L Inferior Frontal Gyrus	09	-42	2	25	-2.98	
14	L Middle Frontal Gyrus	10	-39	38	10	-4.89	1232
15	L Middle Temporal Gyrus	21	-42	5	27	3.23	1635
	L Superior Temporal Gyrus	38	-48	5	-14	4.35	
16	L Supramarginal Gyrus	40	-45	-43	37	-3.90	1849
	L Inferior Parietal Lobule	40	-51	-31	46	-2.81	
17	L Fusiform Gyrus	37	-51	-46	-17	-4.20	606

Tdys= tinnitus-related sentences; Neu= neutral sentences; Gdys= generally negative sentences; R= right; L= left; RSC= retrosplenial cortex; dPCC= dorsal posterior cingulate cortex; vPCC= ventral posterior cingulate cortex; BA= Brodman area.

2. Originalartikel

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Tinnitus- Related Distress: Evidence from fMRI of an Emotional Stroop Task

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Abstract

While chronic tinnitus affects 5% of the population, 17% suffer under the condition. This distress seems mainly to be dependent on negative cognitive-emotional evaluation of the tinnitus and selective attention to the tinnitus. A well-established paradigm to examine selective attention and emotional processing is the Emotional Stroop Task (EST). Recent models of tinnitus distress propose limbic, frontal and parietal regions to be more active in highly distressed tinnitus patients. Only a few studies have compared high and low distressed tinnitus patients. Thus, this study aimed to explore neural correlates of tinnitus-related distress.

Highly distressed tinnitus patients (HDT, n=16), low distressed tinnitus patients (LDT, n=16) and healthy controls (HC, n=16) underwent functional magnetic resonance imaging (fMRI) during an EST, that used tinnitus-related words and neutral words as stimuli. A random effects analysis of the fMRI data was conducted on the basis of the general linear model. Furthermore correlational analyses between the blood oxygen level dependent response and tinnitus distress, loudness, depression, anxiety, vocabulary and hypersensitivity to sound were performed.

Contradictory to the hypothesis, highly distressed patients showed no Stroop effect in their reaction times. As hypothesized HDT and LDT differed in the activation of the right insula and the orbitofrontal cortex. There were no hypothesized differences between HDT and HC. Activation of the orbitofrontal cortex and the right insula were found to correlate with tinnitus distress. The results are partially supported by earlier resting-state studies and corroborate the role of the insula and the orbitofrontal cortex in tinnitus distress.

Keywords: fMRI, tinnitus, distress, Insula, frontal cortex

1.0 Introduction

Tinnitus refers to the perception of sounds with no external origin (Møller 2011). Chronic tinnitus affects approximately 5% of the population (Palmer et al. 2002; Fabijanska et al. 1999). While most individuals habituate to this phantom noise, 17% of the individuals with chronic tinnitus are however severely distressed by the condition (Axelsson and Ringdahl 1989). This distress is not predicted by psychoacoustic qualities of the tinnitus (Henry and Meikle 2000; Hiller and Goebel, 2007), but is rather due to a negative initial cognitive-emotional evaluation of the tinnitus sound (Jastreboff et al. 1996).

Dysfunctional beliefs about tinnitus, attention focus on the tinnitus, dysfunctional coping and avoidance behavior are considered to instigate and maintain tinnitus- related distress (Hallam 1987; Mertin and Kröner-Herwig 1997). Indeed, it has been shown that subjects with unilateral tinnitus pay more attention to the tinnitus ear (Cuny et al. 2004). Furthermore, this attention focus on tinnitus seems to increase tinnitus- related distress (Rief et al. 2004). Concluding from those studies, people with tinnitus focus their attention on the phantom noise and this in turn elevates the tinnitus- related distress. On the other hand, it has been shown that attention to tinnitus is influenced by the amount of tinnitus annoyance (Delb et al. 2008). Thus, attentional bias to tinnitus seems to be influenced by the amount of tinnitus- related distress. Additionally, Andersson and Westin (Andersson and Westin 2008) suggested attention to tinnitus as a mediator for tinnitus- related distress, provided that tinnitus is appraised negatively. This view has been corroborated by a study of Cima and colleagues (Cima et al. 2011), who found an association between catastrophizing and increased attention towards tinnitus in a sample of 61 tinnitus patients and by Andersson and collaborators (Andersson et al. 2006) who could show that attention to tinnitus increased the amount of tinnitus- related thoughts compared to thought- suppression. Thus, there seems to be an association between attention focus to tinnitus and tinnitus- related negative information. Support for this view comes from a study that found a facilitation effect towards tinnitus-related words in comparison to neutral words measured by the Emotional Stroop Task (EST) in a group of tinnitus patients, but not in a control group (Andersson et al. 2005).

The EST is a well- established paradigm to examine emotional processing (Malhi et al. 2005; Posner et al. 2011; Mohanty et al. 2007) and attentional bias (Williams et al. 1996). It has been frequently used in the field of emotional disorders (Williams et al. 1996), and also in chronic pain (Roelofs et al. 2002), which shares common features with tinnitus (Møller 2007; Folmer et al. 2001; Tonndorf 1987). Emotionally salient words should draw attention from the task (color- naming of the words), thus resulting in longer reaction times (Cisler et al. 2011). Generally, studies on the EST find an interference- effect for concern- related words. Andersson et al. (2005) on the other hand found a facilitation effect for tinnitus- related words within a group of tinnitus patients (n=104), but not within a healthy control group (n=21). However, this study had some methodological issues, since the groups were not compared with each other and varied greatly in sample size. Another study on tinnitus patients that used the EST did not find any interference or facilitation effect for tinnitus- related words (Andersson et al. 2000). Thus, there seems to be no clear evidence of an Emotional Stroop effect in tinnitus patients. However, none of these studies controlled for the level of tinnitus-related distress as a potential moderator of effects. Therefore, we expect an Emotional Stroop effect to only occur in highly distressed tinnitus patients. No study known to the authors has ever examined an Emotional Stroop effect in high compared to low distressed tinnitus patients.

Additionally, the emotional processing of tinnitus-related words should heighten the tinnitus annoyance, resulting in the activation of distress-related brain regions. However, little is known about the neural correlates of tinnitus related distress. According to the Global Brain Model (Schlee et al. 2011), damage to the hearing system reduces the sensory input, decreases inhibitory mechanisms in the central auditory system and finally leads to an enhanced excitability of the auditory cortices. This activity in the auditory cortices is supposed to be modulated by a network consisting of frontal, parietal and cingulate regions. The model proposes that this fronto- parietal- cingulate network is more active in highly distressed tinnitus patients. The dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), anterior cingulate (ACC) and the precuneus/posterior cingulate (PCC) are considered as key structures in that network. A resting- state electroencephalography (EEG) study (De Ridder et al. 2011b) identified a component, that differed between high and low distressed tinnitus patients (14- 18 Hz, 22- 26 Hz) that consisted of the medial frontal gyrus, middle frontal gyrus, inferior frontal gyrus, rectal gyrus, ACC, parahippocampal gyrus and the insula. Another resting- state EEG study that compared high and low distressed tinnitus patients (Vanneste et al. 2010) identified four regions that contributed significantly to tinnitus annoyance; the subcallosal ACC, the parahippocampal area, the PCC and the DLPFC. Further support for this model comes from resting- state fMRI- studies. In a mixed sample of bothered and non- bothered tinnitus patients according to the Tinnitus Questionnaire (TQ) (Hallam 1996), tinnitus patients showed higher functional connectivity within an auditory resting-state network in comparison to healthy controls bilaterally in the parahippocampal gyrus, the inferior frontal gyrus, right prefrontal cortex, right inferior parietal lobe and postcentral gyrus (Maudoux et al. 2012). A resting- state fMRI- analysis on bothered tinnitus patients showed greater functional connectivity as compared to HC between the right anterior insula and left inferior frontal gyrus which correlated positively with activity in the auditory cortex (Burton et al. 2012). No differences in functional connectivity could be found in a comparison of non-bothered tinnitus patients and healthy controls (Wineland et al. 2012). Thus, these studies confirmed the role of frontal and limbic structures in tinnitus distress and to some extent in parietal areas. A resting state MEG study found a correlation between the strength of inflow to the temporal cortices and tinnitus annoyance. The temporal cortices received that input from the prefrontal cortex (PFC), cuneus, precuneus and PCC (Schlee et al. 2009). Hence, corroborating a role of the precuneus in tinnitus annoyance.

Recently, it has been suggested that several overlapping brain networks contribute to the perception of tinnitus; the somatosensory cortex, the auditory cortex, a perception network, a salience network, a distress network and memory areas (De Ridder et al. 2011a). Networks of interest for the study of selective attention and distress are the perception network, salience network, the distress network and memory areas. Subgenual ACC, dorsal ACC, PCC, parietal cortex, the precuneus and the frontal cortex form the perception network. Activity within these areas is required to perceive a phantom percept consciously. The salience network, consisting of the dorsal PCC and anterior insula reflects the behavioral significance of the percept. The distress network should include the ACC, anterior insula and amygdala. According to the model memory areas; the parahippocampal area, hippocampus and amygdala, should be associated with awareness to the salient perception and play a role in the reinforcement of annoyance (De Ridder et al. 2011a; Vanneste and De Ridder 2012).

Based on the available empirical evidence regarding tinnitus distress and taking into account the suggestions of the Global Brain Model and the Working Model of Phantom Percepts we hypothesize highly distressed tinnitus patients (HDT) to react slower (interference- effect) to tinnitus-related words as compared to neutral words in an EST and in comparison to low distressed tinnitus patients (LDT) and healthy controls (HC). Additionally, we expect HDT to rate tinnitus- related words as being more negative and arousing in comparison to neutral words and in comparison to LDT and HC. On a neural level we expect HDT to show a higher activity, as measured by blood oxygen level dependent (BOLD) fMRI, in the precuneus, limbic areas and frontal areas in comparison to LDT and HC, especially the parahippocampus, dorsal and subgenual ACC (including anterior and posterior midcingulate cortex), PCC, insula, DLPFC (Brodman Area (BA) 9, 46) and OFC (including inferior frontal gyrus, BA 10, 11, 47).

2.0 Material and Methods

2.1 Sample

A written informed consent from all participants was collected and the study was approved by the ethics committee of the medical department of the University of Göttingen.

Participants were recruited for participation in the study via regional newspapers, the homepage of the German Tinnitus League, flyers and word of mouth. Inclusion criteria were a chronic tinnitus, defined as a constant noise in the ear(s) or the head for at least one year and German as the first language. Exclusion criteria were age above 70, a current major depressive syndrom, hyperacusis, current treatment with psychotropic drugs, days without tinnitus perception, tinnitus perception only in total silence, residual inhibition > one minute, any counter indications to MR- methodology (e.g. pacemaker) and an actual hearing loss. According to the Guidelines on Non- Physician Care and Medical Aids (Heil- und Hilfsmittelrichtlinien) hearing loss was defined as a loss ≥ 30 dB HL at 2 kHz or in two other frequencies between 0.5 kHz and 3 kHz on the better hearing ear (see Seidler 1996). Participants were allocated to the HDT- group if they achieved a score above 30 (moderate annoyance) in the German version of the TQ (Goebel and Hiller 1998; Hallam 1996). The final sample consisted of 48 participants; 16 HDT, 16 LDT and 16 HC. The groups were matched by age and sex. As expected, HDT had a higher level of tinnitus distress. HDT had higher anxiety and depression scores as measured by the German version of the Hospital Anxiety and Depression Scale (HADS) (Herrmann et al. 1995; Snaith and Zigmond 1994) and higher hypersensitivity to sound scores as measured by a Questionnaire on Hypersensitivity to sound (GÜF) (Nelting and Finlayson 2004) than LDT and HC. In comparison to LDT, HDT had a lower vocabulary test score in a subtest of the Hamburg Wechsler Intelligence Test (Tewes 1991). The three groups did not differ with regard to age, sex, tinnitus loudness and hearing loss (see table 1 and figure 1 for details) (Please see the assessment section for details about the instruments).

Insert table 1 here

2.2 Experimental Design

The Emotional Stroop Task comprised of two conditions; tinnitus- related words (TW) and neutral words (NW). The stimuli were presented in a block- design with six blocks per stimulus category. Within one block, each word was presented for 1750 ms in one of four colors (red, blue, green, yellow), followed by a fixation cross (250 ms). The words were presented in a randomized order and each word was presented twice per block. Thus, the length of each block was 24 sec. Neutral blocks alternated with blocks of TW. Before and after each block a fixation cross was presented for 24 sec. Participants were instructed to identify the color of each word by pressing a button on a four- button- response- pad by using the index- and middle- finger of each hand. Inside the MRI- scanner the stimuli were presented on a set of MRI- suited LCD- goggles (resolution 800 x 600; Resonance Technology, Northridge, CA, USA). If needed, the goggles were combined with corrective lenses to ensure corrected to normal vision. All participants wore headphones for communication with the experimenter and noise protection. Additionally, the participants underwent a masking and an emotional sentence task (Golm et al. 2013) in the scanner, which is not presented in this article. The total scan time was approximately 60 minutes. Thus, the study had a 2x3 quasi- experimental design with the within subject factor *word category* (TW, NW) and the between subject factor *group* (HDT, LDT, HC).

All stimuli had been selected previously in two pilot studies (unpublished data). In a first pilot study the valence of 69 words potentially relevant to tinnitus distress and 69 neutral words (matched for frequency of occurrence in German language, number of letters and syllables) was rated by 122 participants. Those participants were distributed evenly between three groups: high distressed tinnitus patients (TQ III and IV), low distressed tinnitus patients (TQ I and II) and healthy controls. The words were derived from the TQ, previous research, patient reports and interviews with medical and psychological tinnitus experts. From this study 28, emotionally relevant tinnitus words and 28 matched neutral words were selected. Emotional relevance was defined as a higher negative valence of the tinnitus- related words within the highly distressed group (maximized difference between the tinnitus and the neutral word) and also in comparison to the other two groups. In a second pilot study, 53 participants underwent an Emotional Stroop Task, 16 highly distressed tinnitus patients, 18 patients with low tinnitus distress and 19 healthy controls. Based on the results of the Stroop task, the six words with the biggest interference effect (response time to TW – response time to matched NW > 40ms) within the HDT- group and with no interference effect in the LDT- and HC-group were selected for this study (see table 2; Meinhardt-Renner and Kröner-Herwig unpublished).

Insert table 2 here

2.3 Assessment of psychosocial variables and audiological information

Tinnitus related distress

The TQ (Goebel and Hiller 1998) is a self- report questionnaire consisting of 52 items. A total score of 0 to 30 corresponds to mild distress, a score between 31 and 46 matches moderate distress, a score of 47 to 59 corresponds to severe distress and a score of 60 and above is considered as very severe tinnitus distress (Goebel and Hiller 1998). The test- retest reliability of $r_{tt} = 0.94$ (Hiller et al. 1994) can be considered as very good.

Determination of exclusion criteria

The German version of the Patient Health Questionnaire (Gräfe et al. 2004; Spitzer et al. 1999) assesses diagnostic information about psychopathology and was used to exclude a major depressive syndrom and concurrent psychotropic medication. The Structured Tinnitus Interview (Strukturiertes Tinnitus Interview) (Goebel and Hiller 2001) assesses detailed information about tinnitus and associated symptoms, such as hyperacusis, hearing loss and vertigo. It was used to exclude hyperacusis, hearing loss, acute tinnitus, non- continuous tinnitus and perception of tinnitus only in total silence.

An audiological evaluation was conducted to further exclude hearing loss and residual inhibition > one minute. Hearing level, minimal masking level, loudness discomfort level, residual inhibition, tinnitus pitch and loudness were assessed. With the exception of the hearing level and tinnitus loudness those features are not of any interest for the current study. The assessment was conducted in the clinical Department of Otorhinolaryngology of the University of Göttingen.

Sample characterization

Anxiety and depression scores were assessed with the German version of the HADS (Herrmann et al. 1995; Snaith and Zigmond 1994). Both subscales consist of seven items with a satisfactory internal consistency (anxiety subscale: $\alpha = 0.80$, depression subscale: $\alpha = 0.81$) and convergent validity (anxiety subscale: $r = 0.65$, depression subscale: $r = 0.70$). The scale has originally been developed for patients suffering from chronic medical conditions (Herrmann et al. 1995).

Hypersensitivity to sounds was assessed with the GÜF (Nelting and Finlayson 2004). The questionnaire consists of 15 items and has a maximum score of 45; a score of 0- 9 corresponds to mild hypersensitivity to sounds, 10 to 15 is considered as moderate, a score between 16 and 23 severe and 24 and above represents very severe hypersensitivity to sounds. Internal consistency for the subscales ranges between .77 and .82.

Behavioral data

To measure valence and arousal of the stimuli, the tinnitus and neutral words were rated on a computerized version of the Self- Assessment Manikin (Bradley and Lang 1994; Barke et al. 2011). The lower the values on the 9- point valence scale, the more negative a word is evaluated (1= very negative, 9= very positive). The higher the ratings on the 9- point arousal scale, the higher the arousal (1=not arousing, 9= very arousing). In order to test for an Emotional Stroop effect, response times of the color naming of the words were recorded during the MRI- scan.

Control variables

The vocabulary subtest (VT) of the Hamburg Wechsler Intelligence Test (Tewes 1991) was performed to control for differences in vocabulary, since novelty of words might act as a confounding variable (Saykin et al. 1999).

2.4 Image acquisition

MR imaging took place on a 3 T MRI- scanner (Siemens Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany). An 8- channel standard phased- array head coil was used (for one participant a 12- channel head coil was used due to head size). Firstly, an anatomical 3D T1- weighted dataset was attained (Turbo fast low angle shot (Turbo FLASH), echo time (TE): 3.26 ms, repetition time (TR): 2250 ms, inversion time: 900 ms, flip angle 12°) that covered the whole head at 1 x 1 x 1 mm^3 isotropic resolution. T2*- weighted gradient- echo echo- planar imaging was used to acquire the functional datasets (TE: 36 ms, TR: 2000 ms, flip angle 90°, 22 slices of 4 mm thickness at an in- plane resolution of 2 x 2 mm²). Within one functional run 302 whole brain volumes were recorded.

2.5 Procedure

Participants, who wanted to take part in the study, underwent a telephone- screening, which included questions regarding exclusion and inclusion criteria and the structured interview about tinnitus. Then, the participants were sent the following questionnaires: TQ, HADS- D, PHQ- D, GÜF and a specifically designed questionnaire to further assess MRI- specific exclusion criteria. In a next step the participants underwent the audiological examination (see above), which took part within one week before the MRI- examination. Before entering the MRI the participants underwent a pre- training to get familiar with the procedure. The Emotional Stroop pre- training consisted of four neutral words naming punctuation marks (Punkt (dot), Komma (comma), Fragezeichen (question mark), Klammer (bracket)) that appeared randomly in one of four different colors (red, blue, green, yellow). The participants were instructed to identify the colors via button press on a keyboard. The participants heard a feedback sound in case of a wrong or missing answer. After each block (16 trials, each word in each color) the instruction appeared again. The training program continued until the participant completed one run without mistakes to ensure all participants had successfully learned which buttons corresponded to which colors. After the pre- training the participants completed the EST inside the MRI- scanner without feedback. After the scanning procedure all participants evaluated the stimuli with the computerized version of the self- assessment Mannequin for arousal and valence and filled in the TQ for a second time. Additionally, the participants completed a vocabulary test, which was conducted via telephone on a later date, since they could be exhausted after the MRI- procedure.

2.6 Statistical procedure

Behavioral Data

The software STATISTICA (Version 10, Stat Soft. Inc., Tulsa, USA) was used to analyze the behavioral data. Regarding the reaction times in the Stroop Task and the ratings of valence and arousal three 3 x 2 repeated measures ANOVAs were performed with the between factor *group* (HDT, LDT, HC) and the within factor *word category* (TW, NW). If the sphericity assumption was violated, Greenhouse- Geisser corrections were performed. LSD- post- hoc-tests were performed and P was set at .05. As measure of dispersion the standard deviation of the mean was used throughout.

Functional Imaging Data

The fMRI data was analyzed with Brain Voyager QX Software version 2.0.8 (Brain Innovation, Maastricht, The Netherlands). Standard preprocessing was performed (3D motion correction, slice scan- time correction, temporal filtering (linear trend removal and high pass filtering) and spatial smoothing with a Gaussian kernel (full width at half maximum 8 x 8 x 8 mm³). On the basis of the general linear model, a random effects group analysis was performed. Only words to which participants responded correctly were used as predictors. Word stimuli with wrong or missing responses were included as confounding variables in the model. The effects of the 1750 ms presentation of the words were convolved with the canonical hemodynamic response function and analyses of planned contrasts were performed. Cluster level threshold estimation was used to correct for multiple comparisons (Forman et al. 1995; Goebel et al. 2006). The uncorrected cluster threshold was set at P = .001 for within-group comparisons and correlational analyses (see below) and P = .005 for between- group comparisons. Monte Carlo simulations (1000 iterations) were performed on the basis of the estimated smoothness of the map and the number of activated voxels to determine the minimum cluster size which was required to yield a maximum error rate at the cluster level of $P < .05$. The Talairach Demon (Lancaster et al. 1997; Lancaster et al. 2000) was used to identify activations by nearest coordinates. In accordance with the Four- Region Neurobiological Model (Vogt et al. 2003; Vogt et al. 2004; Vogt 2005) activations located in the cingulate gyrus were allocated to its subdivisions. Furthermore, the predictors for the contrast TW > NW were extracted and correlated with the individual TQ scores, HADS- depression and HADS- anxiety scores, the vocabulary test scores and the loudness of the tinnitus as assessed via tinnitus loudness matching (in dB HL). In the case of bilateral tinnitus, the louder tinnitus was included. Since there were differences between the groups in terms of vocabulary, anxiety and depression, those scores were included in a correlational analysis to check for potentially confounding effects. Tinnitus loudness was included to check for effects of salience. Recently, it has been suggested that the pain- matrix is not specific for nociceptive stimuli but reflects a salience detection system (Iannetti and Mouraux 2010; Legrain et al. 2011; Mouraux et al. 2011). Therefore, in order to determine whether our effects are specific to the distress network we included a correlation with tinnitus loudness to explore activations within the salience network.

3.0 Results

3.1 Behavioral Data

Reaction Times, Valence and Arousal

It was expected that HDT would show slower reaction times to TW in comparison to NW. This difference should be greater for HDT in comparison to LDT and HC. A repeated measure ANOVA showed no main effect for group or word category, but a group x word category interaction; however LSD- post- hoc- tests revealed no differences within the HDT and LDT, but within the HC (see figure 2 and table 3 for details).

Two repeated measures ANOVAs were conducted to assess differences with regard to valence and arousal ratings of the stimuli. According to valence and arousal we found a main effect for word category but no effect for group or a group x word category interaction. Thus, TW were rated more negative and arousing in comparison to NW (see table 3 and figure 3 for details).

Insert table 3 here

Insert figure 2 here

Insert figure 3 here

3.2 FMRI Data

Within group analysis

Within each group the BOLD- response to TW was compared with the brain activity in reaction to NW. Within the HDT group we expected a higher BOLD- response in the precuneus, limbic and frontal areas, such as the cingulate gyrus, the parahippocampus, the insula, DLPFC and OFC. With regard to our hypothesis a higher BOLD- response to TW as compared to NW within the HDT group could be found in the right insula, right DLPFC and the right precuneus. The HC group showed higher activations to TW in right middle frontal regions, and higher activations to NW in the the left dorsal PCC and right subgenual ACC. LDT only showed higher activations to NW in the right perigenual ACC and left dorsal PCC (see table 4 and figure 4 for details).

Insert table 4

Insert figure 4

Between group analysis

It was expected to find higher BOLD- responses in the hypothesized areas to TW in comparison to NW in HDT as compared to LDT and HC. We failed to find any differences in those regions when comparing HDT and HC, however we found a higher activation in the right insula and the OFC in the HDT group as compared to the LDT group (see table 5 and figure 5 for details). Figure 6 shows the percent signal change of the right insula and the orbitofrontal cortex.

Insert table 5 here

Insert figure 5 here

Insert figure 6 here

Correlational analysis

We further correlated the beta weights for the contrast TW > NW with tinnitus distress within the tinnitus group (HDT and LDT). Furthermore, correlations were computed with tinnitus loudness and all variables that differed between HDT and LDT. Correlations were only found with tinnitus distress and with depression. With regard to hypothesized regions, positive correlations with tinnitus distress were found for the right insula and the right inferior frontal gyrus as part of the OFC. Depression correlated positively with activity in the right insula and the left dorsal PCC (see table 6 and figure 7 for details).

Insert table 6 here

Insert figure 7 here

4.0 Discussion

The aim of the study was to examine possible effects of selective attention and the emotional processing of tinnitus- related words and their relation to tinnitus distress. Therefore an EST was conducted and the neural activity elicited by TW was compared to the neural response to NW within the HDT group and in comparison to LDT and HC. Furthermore the BOLD-response to tinnitus words was correlated with tinnitus distress, tinnitus loudness, vocabulary, depression, anxiety and hypersensitivity to sound. It was expected to find longer reaction times between TW and NW within HDT and in comparison to LDT and HC. Furthermore HDT should evaluate TW as more arousing and negative than NW and compared to the other two groups. However, we did not find any hypothesized effects of response times, nor did we find differences between HDT and the other two groups with regard to valence and arousal. All groups rated TW as more negative and arousing as compared to NW. On a neural level though, the HDT group showed a higher activation in the right insula and bilaterally in the OFC as compared to LDT. Furthermore, tinnitus distress correlated positively with the BOLD- response in the right insula and the right inferior frontal gyrus as part of the OFC. Activity in the right insula and the left dorsal PCC correlated positively with depression. Contradictory to our predictions we did not find differences between HDT and HC in any of the hypothesized regions. Thus, on a neural level our hypotheses have been partially supported.

The lack of an Emotional Stroop effect in HDT

Possible explanations for the lack of an Emotional Stroop effect are the response modality, type of stimuli and the infeasibility of the visual modality to examine effects of selective attention in tinnitus patients. It has been shown that a response via button-press, as in the current study, leads to smaller interference effects as compared to a vocal response in the original Stroop task (MacLeod 1991). However, since tinnitus is a heterogeneous symptom with great variations in variables such as tinnitus location and tinnitus pitch (Møller 2011b) standardized stimuli might not be the best choice. Idiosyncratic word stimuli which are more relevant to the individual emotional concerns (e.g. worries about the tinnitus) of each tinnitus patient could lead to better results. Studies using idiosyncratic word stimuli found Stroop effects in various areas such as posttraumatic stress disorder (Kaspi et al. 1995), obsessive-compulsive disorder (Amir et al. 2009) and healthy subjects (Riemann and McNally 1995). However, no Emotional Stroop effect could be found in chronic pain patients (Roelofs et al. 2005), who share common features with tinnitus patients (Møller 2007; Folmer et al. 2001; Tonndorf 1997), though idiographic stimuli had been used.

Thus, paradigms that examine auditory selective attention might be more suitable to find differences not only on a neural, but also on a behavioral level. For example, in a dichotic listening task it has been shown that alcohol- dependent inpatients show more shadowing errors in comparison to social drinkers when concern- related words were presented in the irrelevant channel as compared to neutral words (Stetter et al. 1994). In an associative learning procedure (Bröckelmann et al. 2011), 42 different click- like tones were conditioned with positive, negative or neutral sounds from the International Affective Digitized Sounds system (Bradley and Lang 2000). Magnetencephalography showed an intensified processing of tones associated with emotional sounds (negative or positive) as compared to neutral sounds in frontal, parietal and auditory sensory areas. Thus, dichotic listening tasks that use tinnitus- related words or affective conditioning paradigms might be another possibility to examine effects of selective attention in tinnitus patients. However, a third possibility, which we cannot rule out in this study, might be a lack of power, since the only study, which found a facilitation effect in tinnitus- patients for tinnitus- related words consisted of 104 participants.

Though the current study did not find an interference effect, the fMRI- results can still be interpreted as neural correlates of tinnitus-related distress. An example from EEG-experiments even shows that neural responses could be more sensitive than reaction times (Heil and Rolke 2004; Heil et al. 2004). The N400 differentiated well between two conditions (semantically related vs. unrelated) in a letter-search priming paradigm in the absence of a reaction time effect, indicating a semantic context effect (Heil et al. 2004). Thus, the authors believe that the results indicate the emotional processing of tinnitus- related words; however the emotional salience of those words obviously was not strong enough to interfere with the task. Thus future studies should use individual tinnitus words to ensure a high personal relevance of the stimuli as discussed above.

Differences between the groups

The amount of personal relevance of the stimuli could also explain the lack of hypothesized differences between HDT and HC, since the TW could not only be interpreted as tinnitus associated stimuli, but also by HC as generally negative characteristics (e.g. a shrill voice). This view is supported by earlier results, in which HDT showed among others a higher activation in the right insula to tinnitus- related sentences as compared to neutral sentences within their group and in comparison to HC (Golm et al. 2013). The sentences provided a clear tinnitus context (e.g. *I will never get rid of the tinnitus*). Furthermore, the personal relevance of the sentences was rated and HDT evaluated tinnitus- related sentences as being more personally relevant in comparison to generally negative sentences, additionally they rated tinnitus sentences higher as compared to HC. HC however evaluated neutral sentences as more personally relevant than tinnitus- related and generally negative sentences. Thus, it might indeed be beneficial for future studies to include tinnitus- related words which are personally relevant to tinnitus patients but not for HC.

However, a number of resting- state studies, as mentioned above, found those differences. Thus, this finding might also be due to the methodology of a task- driven approach. LDT might have actively avoided the tinnitus words. This view is supported by the percent signal change in the OFC. While HDT tend to show higher activations to TW as compared to NW, this pattern seems to be reversed in low distressed patients. It has been shown before that reappraisal, as a strategy of emotional regulation, could lower the activation within the orbitofrontal cortex (Ochsner et al. 2002) and the insula (Goldin et al. 2008). Thus, an additional down- regulation of negative emotions in the low distressed group could explain the differences between HDT and LDT.

Tinnitus Distress and Depression

Activity in the right insula correlated with both; tinnitus distress and depression. Recently, using partial correlations, it has been found that tinnitus distress correlated exclusively with current density distribution in alpha 2, beta 1 and beta 2 activity of the *right* OFC and frontopolar cortex and beta 2 activation of the ACC. Depression scores however correlated with alpha 2 activity in the *left* OFC and frontopolar cortex (Joos et al. 2012). This lateralization effect could however not be confirmed in this study. A recently conducted meta-analysis (Hamilton et al. 2012) showed that depressed individuals show a higher activation to negative stimuli in the amygdala, insula and dorsal ACC and a lower activation in the dorsal striatum and DLPFC as compared to healthy controls. Our results suggest the insula to play a major role in the distress network; however this activation seems not to be specific for distress, but also for depression. It has been shown before that tinnitus distress and depression are associated with each other in a 2- year longitudinal study on 6215 people from the Swedish working population (Hébert et al. 2012). Furthermore, the HDT and the LDT group differed not only with regard to tinnitus distress, but also in depression, anxiety, vocabulary and hypersensitivity to sounds. However, aside from depression, none of these variables correlated with the BOLD- response. Thus, it may be that tinnitus distress and depression activate overlapping brain networks; an idea which has been proposed earlier (Langguth and Landgrebe 2011) and which is conform with the assumption of an unspecific distress network (De Ridder 2011).

Multiple overlapping networks

Since we tested HDT and LDT, the distress network, which according to De Ridder et al. (De Ridder et al. 2011b) includes the anterior insula, amygdala and ACC, should be more active in HDT. Indeed we found the right insula to be more active within HDT and in comparison to LDT. However, the anterior insula is supposed to be part of the distress *and* the salience network (De Ridder et al. 2011a). According to a meta-analysis about the functional differentiation of the insula (Kurth et al. 2010) the dorsal part of the anterior insula is a highly integrative region of multiple processes, such as emotional-cognitive processing and interoception. The activation of the insula in the current study seems to be located in the central part of the insula, which is associated with interoception (Kurth et al. 2010). Interoception on the other hand is closely linked to the perception of emotions (Gray et al. 2007; Singer et al. 2009; Critchley 2005). Thus, in an experiment in which the heartrate-feedback was manipulated, participants evaluated neutral faces as being more emotional, if they received a false feedback of an accelerated heartbeat. Higher activity within the right anterior insula was associated with higher emotionality ratings during false feedback (Gray et al. 2007).

In the field of pain research it has been suggested that the so- called pain- matrix does not reflect activations specific to nociceptive stimulation but rather the behavioral significance of a stimulus regardless of its modality (Iannetti et al. 2010; Legrain et al. 2011; Mouraux et al. 2011). In the field of tinnitus research it might also be important to differentiate between the salience of tinnitus, which could be reflected by its loudness and tinnitus distress. We, however, found a correlation between the BOLD- response in the right insula and tinnitus distress, but not with tinnitus loudness. Thus, the activation of the right insula in our sample might indeed reflect tinnitus distress rather than its salience.

Limitations

There are some limitations to the current study. A problem which is directly related to tinnitus research might be the scanner noise (Danesh et al. 2003; Lockwood et al. 2004). The scanner noise could mask the participant’s tinnitus (Danesh et al. 2003) and even have differential effects on non- auditory brain areas subject to the cognitive demand of the task (Tomasi et al. 2005). Since our study used verbal material it was not important whether the tinnitus was masked by the scanner noise. Furthermore we did not vary the cognitive demand of tasks between the groups, since both groups saw exactly the same stimuli and were given the same instructions. In addition, we controlled for hearing loss. Thus, differential effects of scanner noise are unlikely. Another issue could be the level of distress in the HDT group, since most of the participants in this group had only moderate levels of tinnitus distress. However, moderately distressed tinnitus patients often take part in studies on the effect of cognitive-behavioral therapies that aim to reduce tinnitus- related distress (Kröner-Herwig et al. 2003; Zachriat and Kröner-Herwig 2004; Rief et al. 2005). This indicates that moderately distressed tinnitus patients differ from LDT in their help seeking behavior.

Implications for future studies

For future studies of the neural correlates of tinnitus distress, a combination of resting- state and task- driven fMRI approaches might be useful to make the results more comparable. The resting- state could be assessed via EEG and fMRI. Idiosyncratic word stimuli relevant to tinnitus- related concerns should be used as stimulus material in a sample of HDT who should be scanned twice; before and after a cognitive behavioral intervention. Cognitive- behavioral interventions would be the method of choice, since they have reliably shown to be effective in reducing tinnitus- related distress (Hesser et al. 2011). A repeated measures design pre and post therapy would have the advantage of investigating changes in the distress network and help to identify cortical hubs in tinnitus distress. Furthermore it would help to compare resting- state analysis with a task- driven approach.

Conclusion

Tinnitus-related words seem to activate the distress network in HDT. The roles of the insula and the OFC in the distress network have been confirmed by a task-driven fMRI-approach. Additionally, LDT seem to actively avoid tinnitus-related stimuli. The distress network and depression network seem to partially overlap in their activation of the right insula. Prospective studies are needed to further explore the distress network in chronic tinnitus.

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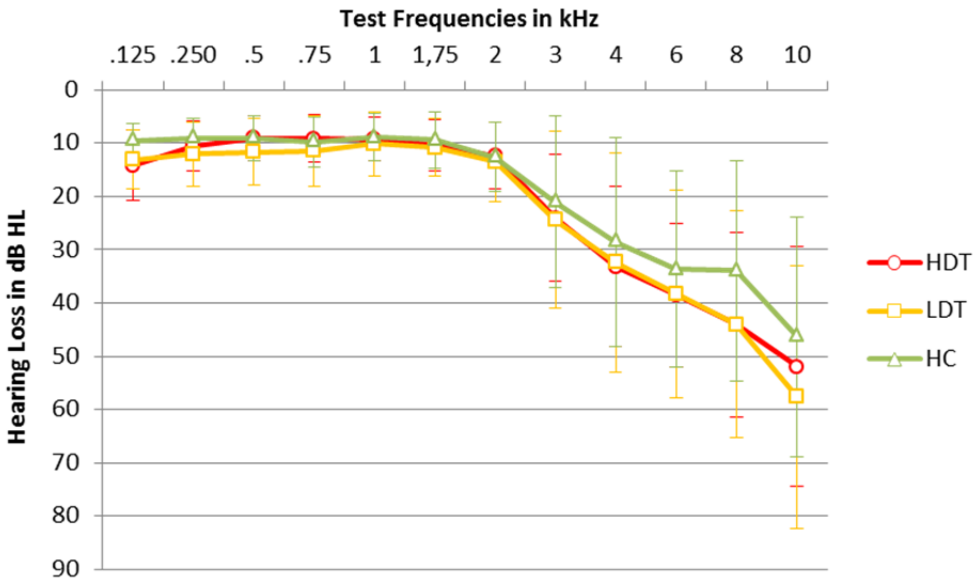
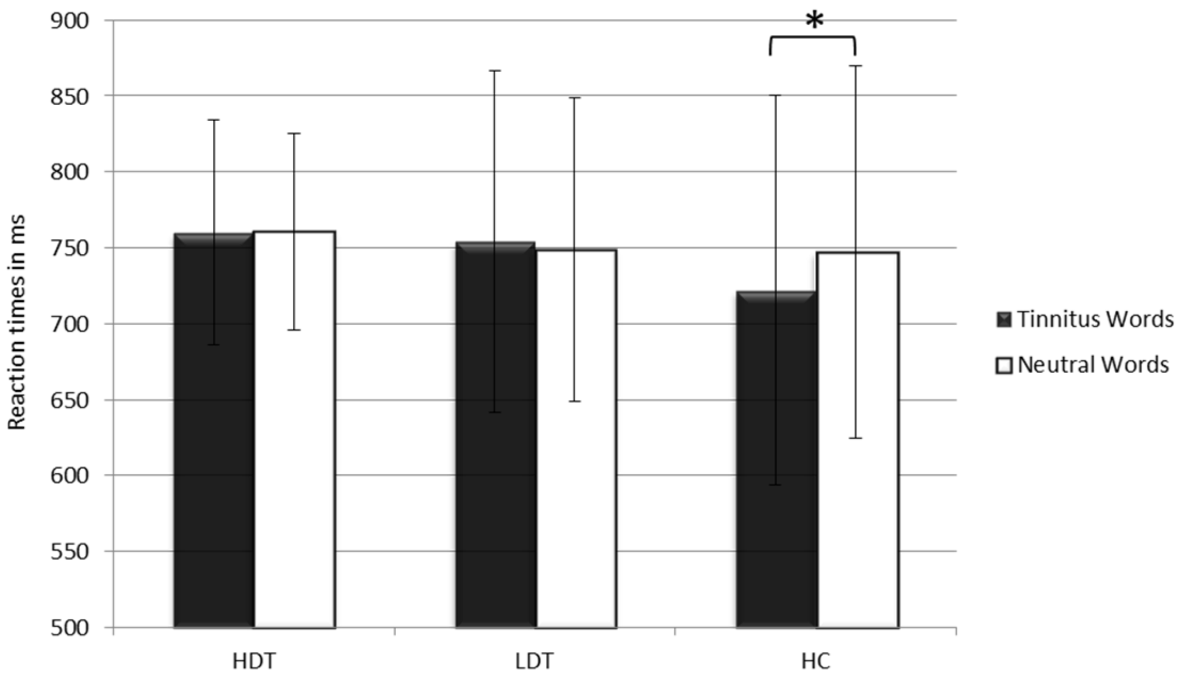
Fig 1 Hearing loss in dB HL



dB= decibel, HC= healthy controls, HDT= highly distressed tinnitus patients, HL= hearing level, LDT= low distressed tinnitus patients, kHz= Kilohertz

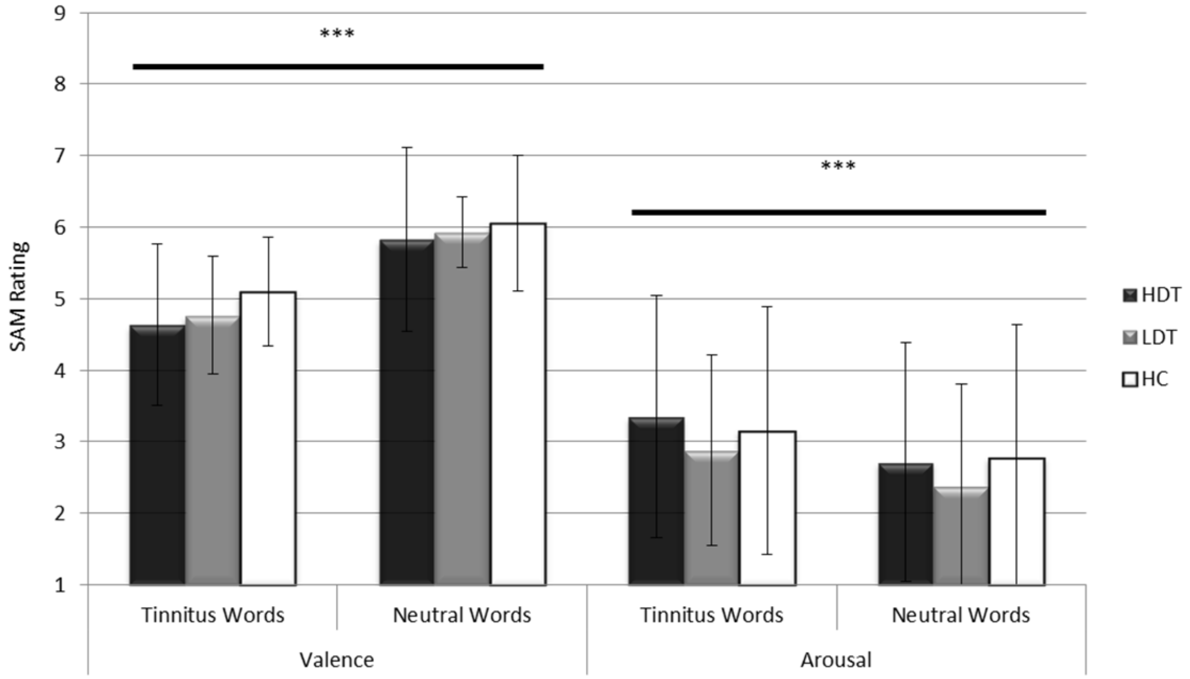
Fig 2 Reaction times in ms



HC= healthy controls, HDT= highly distressed tinnitus patients, LDT= low distressed tinnitus patients, ms= milliseconds, *= $P < 0.05$

Fig 3 SAM- ratings of valence and arousal

Higher ratings correspond to a higher level arousal and a more positive evaluation of the stimuli (valence).



HC= healthy controls, HDT= highly distressed tinnitus patients, LDT= low distressed tinnitus patients, SAM= Self-Assessment-Manikin, ***= $P < 0.001$

Fig 4 Within group results for HDT (top), LDT (middle) and HC (bottom) in the contrast TW - NW

The number next to each cluster corresponds to the cluster number in table 4.

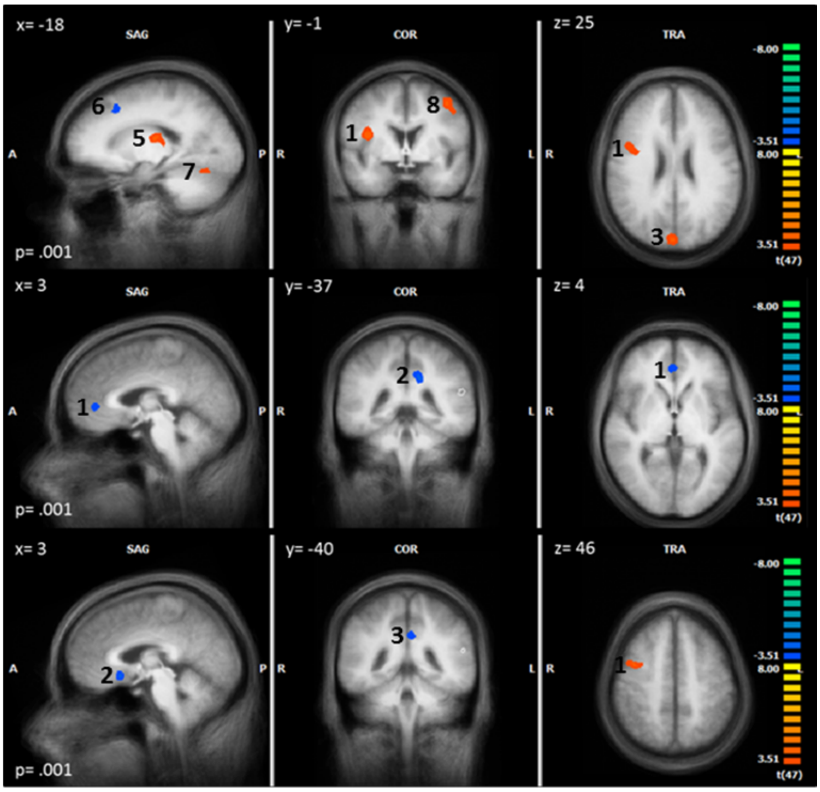


Fig 5 Between group results

The upper shows the contrast TW - NW in HDT vs. LDT (top), and for HDT vs. HC (bottom). The number next to each cluster corresponds to the cluster number in table 5.

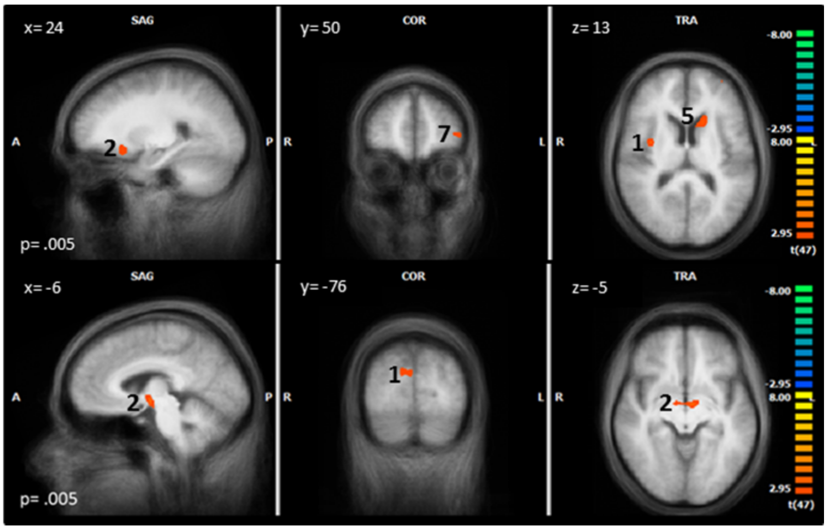
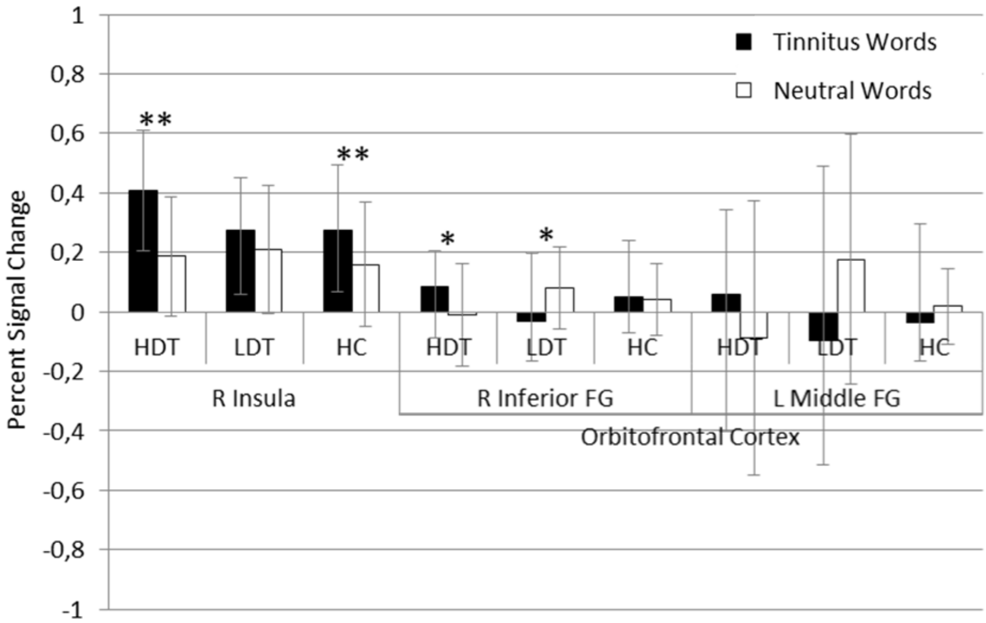


Fig 6 Percent signal change of the right insula and orbitofrontal cortex from the comparison HDT - LDT



FG= frontal gyrus, HC= healthy controls, HDT= highly distressed tinnitus patients, L= left, LDT= low distressed tinnitus patients, R= right, * p< .05, ** p< .01, ◊ p= .05

Fig 7 Correlations with tinnitus distress and depression

The figure shows the correlation between the contrast TW - NW and the TQ- scores (top), and the correlation between TW - NW and the HADS depression scores (bottom) (only tinnitus patients were included). The number next to each cluster corresponds to the cluster number in table 6.

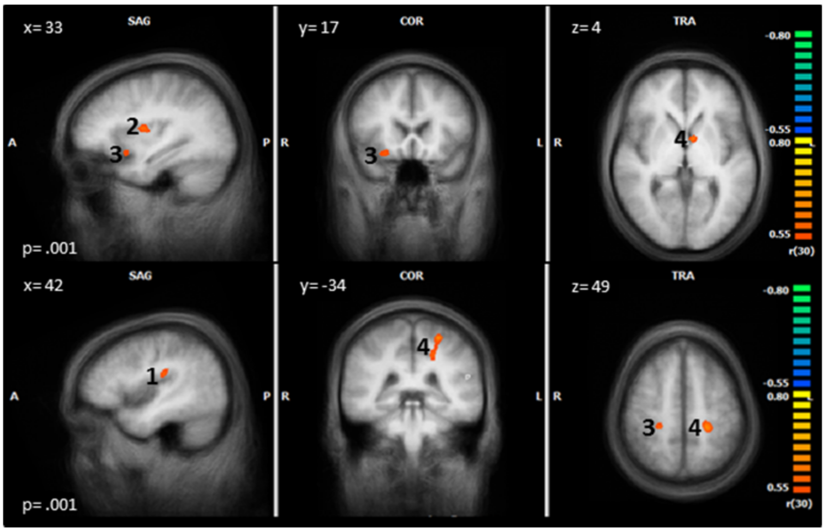


Table 1: Description of the groups and characterizing variables. All t-tests were two-sided.

	HDT (n=16; 13♂)		LDT (n=16; 13♂)		HC (n=16; 13♂)		HDT vs. LDT df=30	HDT vs. HC df=30	LDT vs. HC df= 30
	Mean	SD	Mean	SD	Mean	SD	*t (P)*	*t (P)*	*t (P)*
Age	53.38	12.33	52.88	12.14	52.38	9.42	0.12 (0.9088)	0.26 (0.7984)	0.13 (0.8973)
HADS A	8.31	3.42	4.06	3.07	2.75	2.29	3.70 (0.0009)	5.40 (0.0000)	1.37 (0.1805)
HADS D	6.75	3.44	3.38	3.72	2.56	2.58	2.67 (0.0123)	3.90 (0.0005)	0.72 (0.4786)
VT	20.0	5.37	24.38	4.11	21.94	4.20	- 2.59 (0.0147)	- 1.14 (0.2646)	1.66 (0.1077)
GÜF	13.19	8.16	6.06	5.63	2.56	2.22	2.88 (0.0074)	5.03 (0.0000)	2.31 (0.0277)
Hearing Loss	22.23	6.77	23.28	10.41	19.31	9.09	- 0.34 (0.7365)	1.03 (0.3120)	-0.34 (0.7365)
TQ[a]	40.0	6.69	15.0	6.28			10.89 (0.0000)		
Loudness	39.75	20.99	49.94	20.77			- 1.38 (0.1778)		

♂= male, df= degrees of freedom, GÜF= Geräuschüberempfindlichkeitsfragebogen (Questionnaire on Hypersensitivity to Sound), HADS= Hospital Anxiety (A) and Depression (D) Scale, HC= healthy controls, HDT= highly distressed tinnitus patients, LDT= low distressed tinnitus patients, Loudness= maximum (in case of bilateral tinnitus) loudness of the tinnitus in dB HL as measured via matching of the tinnitus to a similar sound, t= t- value, TQ= Tinnitus Questionnaire, VT= Vocabulary Test

a: Due to missing data on the day of the MRI- scan, the missing TQ- score of 4 participants (1 HDT, 3 LDT) was replaced with the TQ- score from the TQ, that had been filled in after the telephone screening.

Table 2: Stimuli: tinnitus and neutral words matched for word length and frequency of occurrence in the German language.

Tinnitus Words	Neutral Words
brummen	Kirsche
to hum	*cherry*
nachdenken	Schubladen
to think about sth.	*drawers*
Nacht	Preis
night	*price*
Rauschen	Pflanzen
static noise	*to plant*
Schrill	Schrank
shrill	*cupboard*
Testbild	Weltmeer
test pattern	*ocean*

Table 3: Behavioral Data

	HDT		LDT		HC		ANOVA Group	ANOVA Word Cat.	ANOVA G ✕ W
	Mean	SD	Mean	SD	Mean	SD	*F* (2, 44)	*F* (1, 44)	*F* (2, 44)
Val TW	4.64	1.13	4.77	0.83	5.09	0.76	0.72	60.30	0.28
Val NW	5.83	1.29	5.93	0.49	6.05	0.95	*P*= 0.4941	*P*= 0.0000	*P*= 0.7555
Arou TW	3.35	1.70	2.88	1.33	3.16	1.73	0.30	12.44	0.28
Arou NW	2.72	1.67	2.38	1.42	2.78	1.85	*P*= 0.7399	*P*= 0.00099	*P*= 0.7544
RT TW	759.96	73.86	754.05	112.60	721.96	128.47	0.26	2.50	4.65
RT NW	760.40	64.60	748.97	99.79	746.82	122.71	*P*= 0.7688	*P*= 0.1212	*P*= 0.0146

Arou= arousal, *F*= F- value, HC= healthy controls, G= Group, HDT= highly distressed tinnitus patients, LDT= low distressed tinnitus patients, NW= neutral words, RT= reaction time, SD= standard deviation, TW= tinnitus words, Val= valence, W= Word Category, Word Cat.= Word Category

Table 4: Peak- voxels of the within- group results of the contrast TW - NW.

Group	Region	BA	Peak Voxel			*t*	Cluster (mm³)
			x	y	z		
HDT	R Inferior Frontal Gyrus	09	45	8	22	4.20	1 (1755)
	R Insula	13	36	- 1	16	4.45	
	R Precentral Gyrus	06	30	- 10	52	3.86	2 (516)
	R Cuneus/ Precuneus	07	6	- 73	34	3.64	3 (1665)
	L Cuneus	19	0	- 82	31	4.10	
	L Cuneus	18	- 3	- 94	11	3.87	
	L Thalamus		- 9	- 7	1	3.98	4 (279)
	L Thalamus		- 15	- 16	13	4.50	5 (985)
	L Superior Frontal Gyrus	08	- 15	24	46	- 4.24	6 (250)
	L Declive		- 18	- 64	- 17	3.83	7 (264)
	L Middle Frontal Gyrus	06	- 39	- 4	46	4.45	8 (1835)
	L Fusiform Gyrus		- 45	- 52	- 17	3.95	9 (268)
LDT	R pACC	32	3	41	4	- 3.86	1 (265)
	L dPCC	31	- 12	- 37	31	- 4.25	2 (368)
HC	R Middle Frontal Gyrus	09	51	11	34	4.09	1 (1245)
	R Middle Frontal Gyrus	06	39	2	46	4.10	
	R sACC	25	3	17	- 8	- 4.26	2 (254)
	L dPCC	31	- 3	- 40	31	- 3.97	3 (376)

BA= Brodman area, dPCC= dorsal posterior cingulate cortex, HC= healthy controls, HDT= highly distressed tinnitus patients, L= left, LDT= low distressed tinnitus patients, pACC= perigenual anterior cingulate cortex, R= right, sACC= Subgenual anterior cingulate cortex*t*= t- value

Table 5: Peak- voxels of the between- group results.

TW - NW	Region	BA	Peak Voxel			*t*	Cluster (mm³)
			x	y	z		
HDT vs. LDT	R Insula	13	33	- 1	13	3.81	1 (215)
	R Inferior Frontal Gyrus	47	24	17	- 8	3.40	2 (439)
	R Cuneus	18	3	- 79	25	3.64	3 (1186)
	L Hypothalamus		- 9	- 4	- 2	4.80	4 (2598)
	L Lentiform Nucleus		- 24	- 10	- 5	3.72	
	L Caudate		- 15	17	13	3.93	5 (385)
	L Postcentral Gyrus	03	- 24	- 30	61	3.90	6 (117)
	L Middle Frontal Gyrus	10	- 39	50	7	3.16	7 (199)
HDT vs. HC	R Hypothalamus		9	- 7	- 8	3.41	1 (877)
	L Hypothalamus		- 6	- 7	- 5	4.16	
	R Cuneus	18	12	- 76	25	3.27	2 (208)

BA= Brodman area, HC= healthy controls, HDT= highly distressed tinnitus patients, L= left, LDT= low distressed tinnitus patients, R= right, *t*= t- value

Table 6: Peak- voxels of the correlations between the contrast TW - NW and TQ- scores, depression scores, anxiety scores, vocabulary test scores, GÜF-scores and maximum tinnitus loudness (in dB).

TW - NW	Region	BA	Peak Voxel			*r* (*P*= .001)	Cluster (mm³)
			x	y	z		
TQ	R Transverse Temporal Gyrus	41	45	- 22	13	0.60	1 (117)
	R Insula	13	33	- 1	13	0.62	2 (217)
	R Inferior Frontal Gyrus	47	24	17	- 11	0.62	3 (269)
	L Caudate		- 6	2	4	0.62	4 (248)
HADS- D	R Insula	13	42	- 22	22	0.61	1 (110)
	R Postcentral Gyrus	03	24	- 28	49	0.60	2 (123)
	L Thalamus		- 12	- 22	13	0.62	3 (129)
	L dPCC	31	- 18	- 34	37	0.60	4 (1503)
	L Postcentral Gyrus	03	- 24	- 31	52	0.70	4
HADS- A	No correlation						
VT	No correlation						
GÜF	No correlation						
Loudness	No correlation						

BA= Brodman area, dPCC= dorsal posterior cingulate cortex, GÜF= Geräuschüberempfindlichkeitsfragebogen (Questionnaire on Hypersensitivity to sound),), HADS= Hospital Anxiety (A) and Depression (D) Scale, L= left, NW= neutral words, *r*= correlation coefficient, R= right, TQ= Tinnitus Questionnaire, TW= tinnitus-related words, VT= vocabulary test

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Publikationen

Zeitschriftenbeiträge (Eigenanteil siehe letzte Seite)

Golm, D., Schmidt-Samoa, C., Dechent, P. & Kröner-Herwig, B. (2013). Neural correlates of tinnitus related distress: An fMRI-study. Hearing Research 295, pp. 87- 99.

Golm, D., Schmidt-Samoa, C., Dechent, P., & Kröner-Herwig, B. (submitted). Tinnitus-Related Distress: Evidence from fMRI of an Emotional Stroop Task.

Nyenhuis, N., Golm, D., & Kröner-Herwig, B. (submitted). A systematic review and meta-analysis on the efficacy of self-help interventions in tinnitus.

Vorträge

Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B. Neural Correlates of Tinnitus Annoyance and its Reduction after Cognitive-Behavioral Training: Results from an Emotional Stroop Task, 12th International Congress of Behavioral Medicine (ISBM), Budapest, August 2012.

Golm, D. Schmidt-Samoa, C., Dechent, P. Kröner-Herwig, B. Neural Correlates of Tinnitus Annoyance: Results from an Emotional Stroop Task. TRI – the international Conference on Tinnitus, Brügge, June 2012

Golm, D., Barke, A., Dittko, N., Tonassi, T., Kröner-Herwig, B. Medically Unexplained Symptoms: Zeigen Personen mit vielen unspezifischen körperlichen Symptomen Defizite in der emotionalen Bewusstheit und der Theory of Mind? 30.Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Luxemburg, May 2012.

Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B. fMRT-Korrelate neuronaler Grundlagen von Tinnitusbelastung. 13. Kongress der Deutschen Gesellschaft für Verhaltensmedizin und Verhaltensmodifikation (DGVM), Luxemburg, October 2011.

Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B. Neural Correlates of Tinnitus Related Distress – An fMRI-Study. Fifth International TRI Tinnitus Conference, Buffalo (NY), August 2011.

Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B. Eine fMRT-Untersuchung neuronaler Korrelate von Tinnitusbelastung anhand der Verarbeitung emotionaler Sätze. 7. Workshopkongress der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Berlin, June 2011.

Golm, D. Meinhardt-Renner, A. Dechent, P. Moser, T. Kröner-Herwig, B. Neural correlates of tinnitus related distress, 11th International Congress of Behavioral Medicine (ISBM), Washington DC, August 2010.

Golm, D. Meinhardt-Renner, A. Dechent, P. Moser, T. Kröner-Herwig, B. Neuronale Korrelate tinnitusbezogener Belastung. 12. Kongress der Deutschen Gesellschaft für Verhaltensmedizin und Verhaltensmodifikation (DGVM), Leipzig, October 2009.

Poster

Golm, D., Dittko, N., Tonassi, T., Kröner-Herwig, B. Medically unexplained symptoms: Do high symptom reporters show deficits in emotional awareness and theory of mind?, 12th International Congress of Behavioral Medicine (ISBM), Budapest, August 2012.

Golm, D. Schmidt-Samoa, C. A. Dechent, P. Kröner-Herwig, B. Neuronale Korrelate der Belastung durch chronischen Tinnitus: Eine fMRT-Untersuchung. Psychologie und Gehirn, Jena, June 2012.

Golm, D. Schmidt-Samoa, C. A. Dechent, P. Kröner-Herwig, B. Neuronale Korrelate von Tinnitusbelastung: Ergebnisse einer emotionalen Stroop Aufgabe. 30.Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Luxemburg, May 2012.

Golm, D. Schmidt-Samoa, C. A. Dechent, P. Kröner-Herwig, B. Eine fMRT-Untersuchung neuronaler Korrelate von Tinnitusbelastung anhand der Verarbeitung emotionaler Sätze. Psychologie und Gehirn, Heidelberg, June 2011.

Golm, D. Meinhardt-Renner, A. Dechent, P. Kröner-Herwig, B. Neural correlates of Tinnitus annoyance: Results from an Emotional Sentence Task. Autumnschool on Cognitive, Affective, and Nociceptive Functioning of the Anterior Cingulate Cortex, Oppurg, October 2010.

Golm, D. Meinhardt-Renner, A. Dechent, P. Moser, T. Kröner-Herwig, B. Zeigen hoch- vs. niedrig belastete Tinnituspatienten einen Emotionalen Stroop Effekt? Eine fMRT-Untersuchung. 28.Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Mainz, October 2010.

Golm, D. Meinhardt-Renner, A. Dechent, P. Moser, T. Kröner-Herwig, B. Untersuchung neuronaler Korrelate affektiver Verarbeitung bei hoch- vs. niedrig belasteten Tinnituspatienten mittels fMRT. 28.Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Mainz, October 2010.