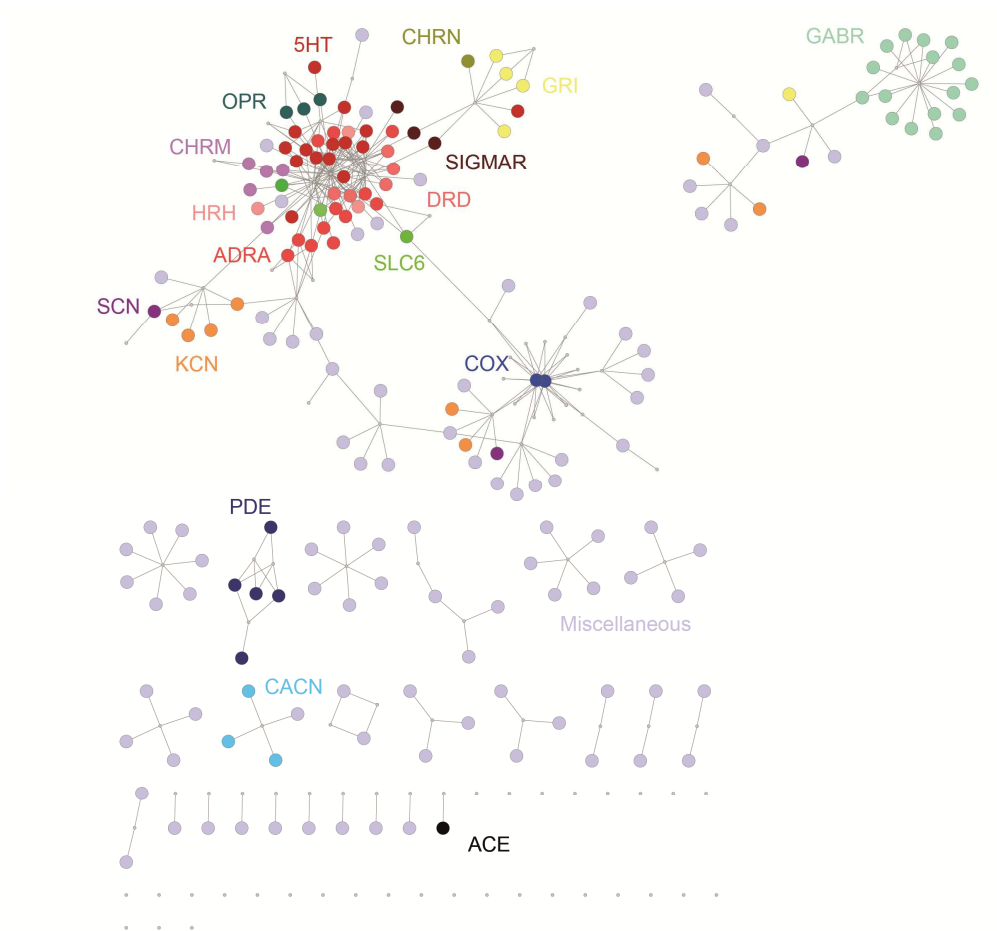
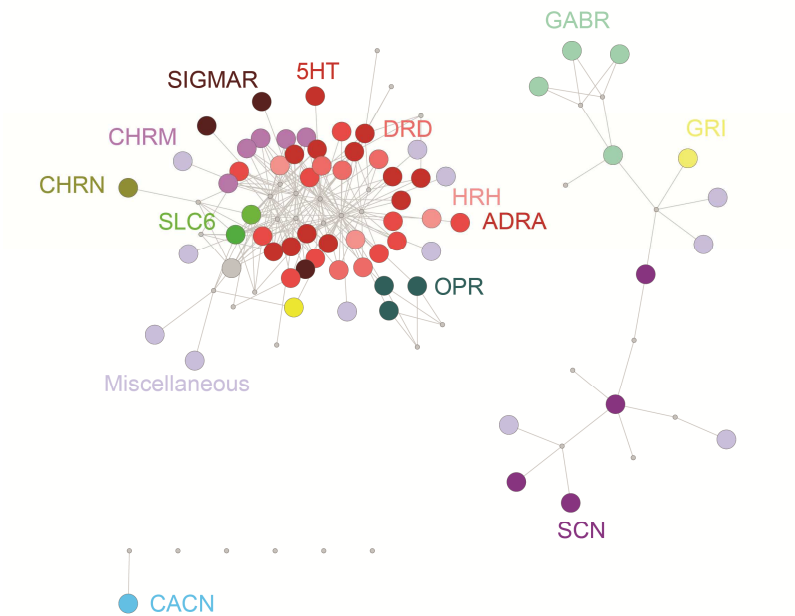


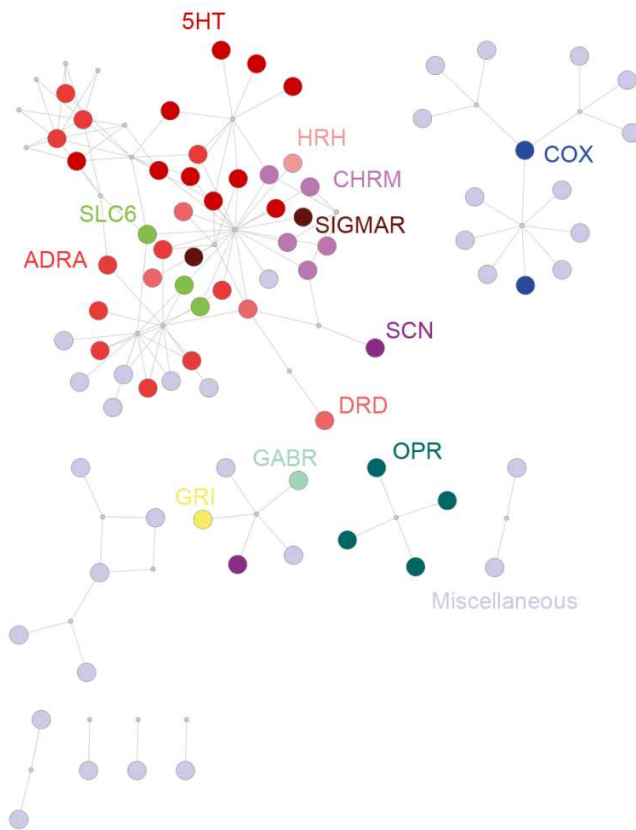
Supplementary Figure S1. Degree of Targets. The number of drugs that aimed each target protein in the tinnitus drug-target network is shown by the grey bars. In black the total number each protein is targeted by drugs in the reference database.



Supplementary Figure S2. Hearing Impaired Target Network. A drug-target network was generated with Cytoscape 3.0, by retrieving all drugs that produce hearing impairment as side effect from SIDER 2 and their targets from DrugBank and PDSP Ki. An edge was placed between a drug node and a target node if the protein is a target of that drug in the reference database. Drug nodes were minimized in order to visualize the tinnitus target space. Targets were color-coded according to protein family members.



Supplementary Figure S3. Hyperacusis Target Network. A drug-target network was generated with Cytoscape 3.0, by retrieving all drugs that produce hyperacusis as side effect from SIDER 2 and their targets from DrugBank and PDSP Ki. An edge was placed between a drug node and a target node if the protein is a target of that drug in the reference database. Drug nodes were minimized in order to visualize the tinnitus target space. Targets were color-coded according to protein family members.



Supplementary Figure S4. Depression Target Network. A drug-target network was generated with Cytoscape 3.0, by retrieving all drugs that produce depression as side effect from SIDER 2 and their targets from DrugBank and PDSP Ki. An edge was placed between a drug node and a target node if the protein is a target of that drug in the reference database. Drug nodes were minimized in order to visualize the tinnitus target space. Targets were color-coded according to protein family members.

Supplementary Table S1: Side effects. Drugs that produce tinnitus, hearing impairment, hyperacusis and depression were downloaded from SIDER 2 (<http://sideeffects.embl.de>) as of September 2012. (See supplementary excel files).

Supplementary Table S2: Number of drugs in the Drug Network

ATC CODE	Total Drugs	Drugs in Giant Component
A: Alimentary tract and metabolism	17	9
B: Blood and blood forming organs	2	0
C: Cardiovascular system	51	36
D: Dermatologicals	6	3
G: Genito-urinary system	10	6
H: Systemic hormonal preparations	2	0
J: Antiinfectives	25	1
L: Antineoplastic	21	8
M: Musculo-skeletal system	25	21
N: Nervous system	94	85
P: Antiparasitic	3	1
R: Respiratory system	8	7
S: Sensory organs	3	2
V: Various	10	1
GRAND TOTAL	277	180

Supplementary Table S3: Drug Targets. Protein targets were extracted from a drug-target reference database built with drugs and targets derived from DrugBank (<http://www.drugbank.ca/>) and the NIMH Psychoactive Drug Screening Program (PDSP) Ki Database (<http://pdsp.med.unc.edu/pdsp.php>), as of September 2012. PubChemID were extracted from <http://pubchem.ncbi.nlm.nih.gov/> and ATC codes from the World Health Organization Center for drug Statistics Methodology http://www.whocc.no/atc_ddd_index/. Column E

indicates the 1st Level ATC code used for color-coding in Figure 1. (See supplementary excel files).

Supplementary Table S4: Target Description. Gene names were according to the National center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/gene>). (See supplementary excel files).

Supplementary Table S5: Tinnitus. Statistical calculations for tinnitus as side effect performed according to Methods. Column B indicates the number of times a target is present in the tinnitus database and C the total times each protein is targeted by drugs in the reference database. Column F, q value after correction for false discovery rate. EF, enhancement factor. (See supplementary excel files).

Supplementary Table S6: Hearing Impaired. Statistical calculations for hearing impairment as side effect performed according to Methods. Column B indicates the number of times a target is present in the tinnitus database and C the total times each protein is targeted by drugs in the reference database. Column F, q value after correction for false discovery rate. EF, enhancement factor. (See supplementary excel files).

Supplementary Table S7: Hyperacusis. Statistical calculations for hyperacusis as side effect performed according to Methods. Column B indicates the number of times a target is present in

the tinnitus database and C the total times each protein is targeted by drugs in the reference database. Column F, q value after correction for false discovery rate. EF, enhancement factor. (See supplementary excel files).

Supplementary Table S8: Depression. Statistical calculations for depression as side effect performed according to Methods. Column B indicates the number of times a target is present in the tinnitus database and C the total times each protein is targeted by drugs in the reference database. Column F, q value after correction for false discovery rate. EF, enhancement factor. (See supplementary excel files).

Supplementary Table S9. PubMed references which support the link of salicylate and suggest the participation of the serotonergic system and voltage-gated sodium channels in tinnitus.

Salicylate	
reviews including animal and human effects	1, 2, 3, 4, 5, 6, 7, 8
as side effect in humans	9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
animal models	21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38
Serotonergic	
increased c-fos expression in gerbil raphe nucleus	39, 40
increased serotonin levels in rat inferior colliculus and auditory cortex	41
increased plasmatic levels of 5-hydroxyindoleacetic acid in humans	42
serotonin reuptake inhibitors in tinnitus treatment	43, 44, 45, 46, 47, 48, 49
Voltage-gated sodium channels	
inhibition of voltage-gated sodium channels in rat inferior colliculus by lidocaine	50
inhibition of voltage-gated channel currents in rat auditory cortex neurons by salicylate	51, 52
changes in expression of voltage-gated channels after acoustic trauma in rat cochlea	53
tinnitus reduction by lidocaine in patients	54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64
tinnitus increase by lidocaine in patients	60, 62
tinnitus reduction by ropivacaine in patients	55
tinnitus reduction by tocainide in patients	65, 66, 67
tinnitus reduction by carbamazepine in patients	68, 69, 70, 71

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