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Maximizing the value of twin studies in health and behaviour

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Supplementary Table 1 | Applications of the classic twin design to network characteristics from Graph Theoretical Analysis for electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and diffusion tensor imaging studies (DTI).

Reference	N (MZ/DZ/no zygosity)	Mean (SD) age	Method	Main Conclusions[a]
Smit et al., 2008[1]	267/307, plus 191 siblings of twins in two age groups	26.2 (4.1) 49.4 (7.2)	EEG: θ, low α, high α, low β, high β power	Across frequency powers, 46–89% of ɣ and 37–62% of λ variances are heritable. For σ, 27-51% of the variance is heritable, besides the high alpha band (0%). Network parameters – viable characteristics of the genetic differences in the brain.
Fornito et al., 2011[2]	32/26/-	MZ 37.8 (13.6) DZ 43.2 (9.9)	fMRI	In the 0.09 – 0.18 Hz frequency interval, genetics account for 60% of CE_{glob} variance. Across brain regions, the genetic influence for network parameters differs from <10% to 81%. Higher h^2 in bilateral posterior cingulate and medial prefrontal cortices, dorsolateral prefrontal and superior parietal cortices, and lateral temporal and inferomedial occipital regions. Nodes of these regions are the potential genetically determined backbone of cost-efficient brain connectivity.
van den Heuvel et al., 2013[3]	42/44/-	12.2 (0.3)	fMRI	Heritability accounts for 42% of variance in E_{glob} but not in ɣ or K. Distinct sets of genes probably control the architecture of brain interactions, but not functional connectivity itself.
Sinclair et al., 2015[4]	168/178/246	23(2.5)	fMRI	Mean ɣ (h^2 range: 47–59%), E_{glob} (h^2 range: 52–64%), σ (h^2 range: 51–59%), and Q (h^2 range: 38–59%) are moderately heritable for density connection of 5-25%. After applying global signal regression, h^2 estimates decrease. Mean ɣ, Q, and E_{glob} have correlated genetic factors. Absence of the genetic influence in φ (h^2 range: 0-29%) argues against the idea of heritable centres of functional networks.
Menardi et al., 2021[5]	16/392/-	MZ 29.0 (2.6) DZ 28.7 (2.4)	fMRI	In one of two datasets, moderate genetic effects were observed in graph theory metrics with the density connection 10%: λ (56%), ɣ (46%), E_{glob} (26%), E_{loc} (38%), and Q (26%), but not for σ. Two out of seven measures of brain network resilience (Targeted Edge Removal (22%), and Critical Point measure (35%)) show

Reference	N (MZ/DZ/no zygosity)	Mean (SD) age	Method	Main Conclusions[a]
				moderate h^2, indicating potential importance of communication pathways and weak connections for network functioning. Results were not confirmed in a second dataset, where only E_{loc} was heritable (21%).
Bohlken et al., 2014[6]	90/66/-	31.9 (13.6)	DTI	λ (57%) and ɣ (68%) are substantially heritable and partly share genetic endowments with white matter volume (16% with ɣ, 19% for λ) and FA of white matter (11 % with ɣ, 15% for λ). There are medium negative genetic correlations between white matter volume (-.43 for λ and -.33 ɣ) and white matter mean FA (-.47 for both λ and ɣ) with both topological network properties.
Koenis et al., 2015[7]	57/63, plus 42 siblings of twins	Twins: 9.9 (1.4) Sibs: 12.9 (1.4)	DTI	E_{glob} and E_{loc} are moderately to highly heritable in weighted networks with mean FA and streamline count networks (locally up to 74% and 64%). For FA-based networks, h^2 increases during early adolescence (from 31% to 48% for E_{glob} and from 37% to 40% for E_{loc}). Over age, a stable genetic factor influenced E_{glob} and E_{loc}. IQ scores and average E_{loc} at age 13 were caused by shared genes (r_g = 1).
Bohlken et al., 2016[8b]	102/98/-	MZ 36.4 (13.1) DZ 36.4 (12.7)	DTI	Additive heritability accounts for 69% of the variance in FA-weighted E_{glob}. FA-weighted E_{glob} and Schizophrenia share a common genetic factor, which accounts for 89% of their association. E_{loc} is negatively associated with the increased liability of Schizophrenia for 14 regions through genetic factors and for seven regions through environmental factors. Genetic liability for Schizophrenia is connected with a decrease in white matter fiber connectivity in frontal and subcortical regions.
Koenis et al., 2018[9]	98/128/-	9.2 (0.2), 12.2 (0.4), 17.2 (0.3)	DTI	At 10, 13, and 18 years, the correlations between FA-weighted E_{glob} and IQ are partly driven by genes and the contribution of genetics to the covariance with IQ increases with age for both E_{loc} and E_{glob}. E_{glob} was significantly heritable during adolescence (47% at age 18). A stable genetic factor influenced E_{glob} over measurements.

[a] θ, theta; α, low and high alpha; β, low and high beta frequency bands: power representing the amount of activity in different frequency bands of the EEG signal. FA = fractional anisotropy: microstructural property, describing the integrity of white matter. r_g = genetic correlation: the extent to which genetic influences on two different traits covary. Clustering coefficient (ɣ) = measure of network segregation calculated from the number of triangles of local

interconnections within three nodes in the network. Characteristic Path Length (λ) = the measure of the functional integration, calculated from the average minimum number of steps required to reach one node from another. Global Efficiency (E_{glob}) = the inverse of the Characteristic Path Length. Local efficiency (E_{loc}) = the inverse of the Characteristic Path Length from a particular node to two of its closest neighbouring nodes. Small-Worldness (σ) = the ratio of Clustering Coefficient and Characteristic Path Length, describing the balance between network integration and segregation. Modularity (Q) = a measure of network segregation which reflects the degree to which a network can be separated into distinct modules based on high connections within modules and fewer connections between modules. Rich Club Coefficient (φ) = reflects the degree to which highly connected or central nodes tend to associate with each other[3]. D_{glob} = the summed physical distance between nodes in the network[1]. Degree and Connection density (K) = the number of binary connections for a particular node and for a whole network, respectively. Cost-Efficiency (CE_{glob}) = measure of the balance between efficiency maximization and minimum connection cost in the network, calculated as max(E_{glob} – connection distance (D_{glob}))/K_{max}[2]. For a more detailed explanation of network parameters, please see Rubinov & Sporns (2010)[10].

[b] Study comprised 37 individuals with a Schizophrenia diagnosis and 163 participants without a psychiatric diagnosis.

Supplementary Table 2 | Proband-wise (or case-wise with full ascertainment) monozygotic (MZ) and dizygotic (DZ) twin concordance rates. Concordance was calculated as 2C/(2C+D), where C is the number of concordant twin pairs and D is the number of discordant twin pairs[11]. Studies that used the proband-wise method were selected, as these estimates are robust to incomplete ascertainment, unlike case-wise and pairwise estimates. This table, with rounded concordance rates, is presented as **Fig. 2a** in the main text.

	Disorder	N pairs (MZ/DZ)	Concordance rate (%)		Reference
			MZ twins	DZ twins	
Metabolic syndrome	Type 1 diabetes	44/183	42.9	7.4	Hyttinen et al., 2003[12]
	Type 2 diabetes	1007/1814	45*	19*	Willemsen et al., 2015[13]
Autoimmune disorders	Rheumatoid arthritis	32/123	9.1	6.4	Svendsen et al., 2013[14]
	Psoriasis	224/580	33	17	Lønnberg et al., 2013[15]
	Crohn's disease	33/50	38	2	Halfvarson, 2011[16]
	Ulcerative colitis	41/49	15	8	Halfvarson, 2011[16]
Neurodegenerative disorders	Alzheimer's disease	F: 655/1009 M: 428/679	F: 61 M: 45	F: 41 M: 19	Gatz et al., 2006[17]
	Parkinson's disease	96/124	20	13	Goldman et al., 2019[18]
	Multiple sclerosis	146/224	25.3	5.4	Willer et al., 2003[19]
Psychiatric disorders	Attention deficit hyperactivity disorder	F: 12/34 M: 42/75	F: 40 M: 44	F: 6 M: 10	Lichtenstein et al., 2010[20]
	Autism spectrum disorder	67/210	93.7	46.7	Rosenberg et al., 2009[21]
	Major depressive disorder	493/970	17*	7*	Wium-Andersen et al., 2020[22]
	Schizophrenia	81/367	33‡	7‡	Hilker et al., 2018[23]
Oncological diseases	Colorectal cancer	601/1207	22*	11*	Graff et al., 2017[24]
	Prostate cancer	990/1827	40	25	Hjelmborg et al., 2014[25]
	Breast cancer	594/1055	28	20	Möller et al., 2016[26]

*Proband-wise rate was not listed in the original study but calculated here as 2C/(2C+D). ‡Estimated using liability threshold models adjusting for censoring with inverse probability weighting. F, female; M, male.

Supplementary Table 3 | Heritability, prevalence, and expected MZ concordance rates of the disorders highlighted in Fig. 2b. The expected MZ concordance rates were calculated based on the formula of Smith (1970)[27].

Disorder[a]	Heritability	World population prevalence	Expected MZ Concordance rate[b]
Alzheimer's disease[b]	58-79%[28]	6-8%[29]	55%
Type 2 diabetes[c]	52-72%[13,30]	10.5%[31]	45%
Schizophrenia[d]	80%[30]	0.33-0.75%[32]	33%
Rheumatoid arthritis	57%[30]	0.46%[33]	13%
Breast cancer	33%[34]	0.048%[35]	4%

[a] In **Fig. 2b**, a heritability of 79% and prevalence of 7% were plotted for Alzheimer's disease, a heritability of 60% was plotted for Type 2 Diabetes, and a prevalence of 0.54% was plotted for Schizophrenia.

[b] Expected MZ concordance rate is calculated based on the formula of Smith (1970)[27]:

$\tan(\frac{\pi}{4}(1 - Rh^2)(1 + Rh^{2^5})) = \log_{10} q_R \div \log_{10} q_P$, where R is the coefficient of relationship, h^2 the heritability of liability, $q_R$the concordance rate, and q_P the prevalence of the disorder.

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