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PROFESSOR DR. MAX CLOËTTA

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Prof. Dr. Andreas Papassotiropoulos
Prof. Dr. Dominique J.-F. de Quervain

«Genetics of Human Memory:
From Gene Hunting to Drug Discovery»

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VORWORT

Professor Adriano Fontana
Präsident des Stiftungsrates

Die Stiftung Professor Dr. Max Cloëtta kann dieses Jahr auf 40 Jahre ihres Wirkens zurückblicken. Sie war 1973 von Dr. Antoine Cloëtta zu Ehren seines Vaters mit der Absicht, die medizinische Forschung zu fördern, gegründet worden. Neben der jährlichen Verleihung eines Preises an hervorragende, jüngere Forscher, finanziert die Stiftung auch Forschungsstellen für Nachwuchskräfte. Diese Förderung erlaubt es erfolgreichen Cloëtta-Stipendiaten, sich eine Basis zur Erlangung einer Professur in der medizinisch-biologischen Forschung zu schaffen.

Die Stiftung Professor Dr. Max Cloëtta zeichnet in diesem Jahr zwei an der Universität Basel tätige Neurowissenschaftler aus: Prof. Dr. med. Andreas Papassotiropoulos und Prof. Dr. med. Dominique J.-F. de Quervain. Ihre herausragende Forschung hat zu neuen Erkenntnissen im Gebiete der neurobiologischen und molekularen Mechanismen des menschlichen Gedächtnisses geführt und das Wissen um die genetischen Grundlagen psychischer Prozesse und deren Störungen bereichert. Die Arbeiten sind in das Gebiet der biologischen Psychiatrie einzuordnen. In deren Mittelpunkt steht das biologische Verständnis von psychischen Erkrankungen. War es bis unlängst die exakte klinische Beobachtung und Beschreibung psychischer Erkrankungen, erlauben es nun neue Technologien, zeitnah die Funktion grösserer Hirnareale zu untersuchen. Die methodischen Durchbrüche wurden durch die Entwicklung der Positronenemissionstomografie (PET), der funktionellen Magnetresonanztomografie und der Magnetenzephalografie (MEG) eingeleitet. Dominique J.-F. de Quervain und Andreas Papassotiropoulos ist es gelungen, die Gedächtnisfunktion und deren Modifikation durch Umwelteinflüsse auf der molekularen Ebene zu charakterisieren und damit etwas Licht in eines der vielen Geheimnisse der Psychiatrie zu bringen. Die Verknüpfung der über Gene gesteuerten neuronalen Prozesse mit dem Gedächtnis und der Erfahrung steht im Mittelpunkt der neurobiologischen Forschung.

Diese ist geneigt in den nächsten Dekaden neue Erkenntnisse zu abnormen Systemabläufen, welche sich hinter psychiatrischen Erkrankungen verbergen, beschreibbar zu machen. Über das biologische Erkennen werden sich neue therapeutische Ansätze in den Gebieten Schizophrenie, Demenz, neurodegenerative Erkrankungen und Persönlichkeitsstörungen finden lassen.

Aus der Sicht der Stiftung Professor Dr. Max Cloëtta ist es bemerkenswert, dass in den 40 Jahren ihres Bestehens unter den insgesamt 70 ausgezeichneten Forscherpersönlichkeiten 14 (20 %) der Preisträger im Bereich der Neurobiologie tätig waren. Dies widerspiegelt auch die hervorragende Stellung der Neurobiologie in der Schweiz. Letzteres zeigt sich ganz eindrücklich in der Analyse von 6518 Arbeiten, die im Gebiete der Neurobiologie in den Jahren 2000 und 2010 publiziert wurden. Diese führten pro Publikation zu 22.0 Zitationen. Damit nimmt die Schweiz Rang 3 ein. Die Plätze 1 und 2 gingen an England und die USA mit 24.5 resp. 24.0 Zitationen pro Arbeit. Ein Blick auf das wissenschaftliche Wirken der im Jahr 2013 von der Stiftung Prof. Dr. Max Cloëtta ausgezeichneten Forscher – Prof. Dr. med. Andreas Papassotiropoulos und Prof. Dr. med. Dominique J.-F. de Quervain – zeigt, wie sich die Neurobiologie in der Schweiz u.a. dank Innovation und Vernetzung von Forschungsgruppen mit unterschiedlichen methodischen und denkerischen Ansätzen international weiter hervorragend positioniert.

Prof. Dr. med. Adriano Fontana

Brigitt Küttel
Geschäftsführerin

Stiftungsrat

Nach Drucklegung des Heftes Nr. 40/2012 erreichte uns die traurige Nachricht vom Hinschied unseres langjährigen Stiftungsratsmitglieds Dr. Hans-Ulrich Doerig (Mitglied 1995 – 1997, Vizepräsident 1997 – 2009). Während 14 Jahren hatte Dr. Doerig – neben seinem grossen beruflichen Engagement bei der Credit Suisse – sein profundes Wissen der Stiftung Prof. Dr. Max Cloëtta zur Verfügung gestellt. Dieses, verbunden mit grosser Menschlichkeit und immer wieder der nötigen Prise Humor, bleibt unvergessen. Am 11. Dezember 2012 hat eine grosse Trauergemeinde im Zürcher Fraumünster von Dr. Doerig Abschied genommen. Er hinterlässt eine immense Lücke, und wir werden seiner in Ehren gedenken.
Auch 2013 – vierzig Jahre nach der Errichtung der Stiftung – waren die Finanzen ein wichtiges Thema von Sitzungen und bilateralen Kontakten der Stiftungsratsmitglieder. Im Verlauf verschiedener Verhandlungen gelang es, die Kosten für die Vermögensverwaltung und die Administration in den Griff zu bekommen. Mit der Erschliessung neuer Einnahmequellen und dem Eingehen neuer Partnerschaften soll die Stiftung in die Lage gebracht werden, ihren Auftrag zur Förderung der medizinischen Forschung in der Schweiz weitere Jahrzehnte erfüllen zu können.

Cloëtta-Preis

Bereits zum dritten Mal findet die Preisverleihung des Cloëtta-Preises nicht in Zürich, sondern an der Heimuniversität des Preisträgers statt. Wir sind über diese Neuerung sehr glücklich und sehen den Zweck erfüllt, die Stiftung näher an die Universitäten und damit an die Forschenden zu bringen.

2013 wird erstmals in der Geschichte der Stiftung Prof. Dr. Max Cloëtta ein Forscherduo ausgezeichnet: Prof. Andreas Papassotiropoulos und Prof. Dominique J.-F. de Quervain leiten an der Universität Basel gemeinsam die transfakultäre Forschungsplattform «Molekulare und Kognitive Neurowissenschaften». Um ihrer translational orientierten Forschung zur konkreten therapeutischen Anwendung zu verhelfen, haben sie 2013 die GeneGuide AG gegründet.

Unser grosser Dank gilt Prof. Peter Meier-Abt, dem Vertreter der Universität Basel in unserem Stiftungsrat, sowie den Vertreterinnen und Vertretern der Universität Basel für die tatkräftige Unterstützung bei der Organisation der Feier.

Forschungsstellen

Das Forschungsstellenprogramm ist für die Stiftung Prof. Dr. Max Cloëtta – und für den akademischen Mittelbau in der Schweiz – von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung einem Mangel an Forschernachwuchs in der Schweiz entgegenwirken und den Stelleninhabern helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben.

Im Jahr 2013 finanzierte die Stiftung Professor Dr. Max Cloëtta folgende Forscher an Schweizer Universitäten mit fünf- resp. zweijährigen Grants:

Dr. Rajesh Jayachandran, 1977, Biozentrum der Universität Basel. Projekt: Role for Coronin 1 signaling in the development of autoimmunity and T cell mediated disorders. Unterstützungsdauer 1.7.2011–30.6.2016.
Dr. Daniel Fuster, 1972, Universität Bern, Institut für Biochemie und Molekulare Medizin. Projekt: Novel mammalian sodium/hydrogen ex-

changer family NHA – a quest for biological function. Unterstützungsdauer 1.6.2008 bi 31.5.2014.
Dr. Benjamin Marsland, 1977, Centre Hospitalier Universitaire Vaudois, Service de pneumologie. Projekt: Innate and adaptive immune responses in the lung: implications for protective immunity. Unterstützungsdauer 1.7.2009–30.6.2014.
Dr. Jean-Marc Waldburger, 1970, Laboratoire de Rhumatologie, Département de Pathologie et Immunologie, Centre Médical Universitaire Genève. Projekt: The role of store operated calcium entry in arthritis. Unterstützungsdauer 1.12.2011–30.11.2013.

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia Stiftung, Vaduz, Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss der Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet. Erfreulicherweise konnte der Vertrag mit der Uniscientia Stiftung bis 2015 verlängert werden.

2013 wurden folgende Medizinerinnen und Mediziner unterstützt:

Dr. med. Michael Liebrenz, 1978, Oberarzt. Psychiatrische Universitätsklinik Zürich. Fellowship in Forensic Psychiatry. Gastinstitut: Dept of Psychiatry, Columbia University, New York, USA, 07.2012–06.2013.
Dr. med. Tobias Reichlin, 1979, Assistenzarzt, Universitätsspital Basel, Abt. für Kardiologie. Projekt: Characterization of the epicardial substrate for ventricular arrhythmias. Gastinstitut: Harvard Medical School, Brigham and Woman Hospital Boston, USA, 07.2011–06.2013.
Dr. med. Navarini Alexander, 1976. Oberarzt, Dermatologische Klinik, Universitätsspital Zürich. Projekt: Funktionelle Evaluation einer neu identifizierten Mutation im IL36RN Gen bei der schweren generalisier-

ten pustulösen Psoriasis. Gastinstitut: King's College, Division of Genetics and molecular medicine St. John's Institute, London, UK, 04.2012 – 03.2013.
Dr. med. Heidemarie Gast, 1967, Oberärztin an der Universitätsklinik für Neurologie am Inselspital Bern. Projekt: To investigate the hypothesis that burst firing of single neurons in humans is a marker for seizure suppressive state. Gastinstitut: Klinik für Epileptologie, Universität Bonn, DE, 06.2013–05.2014.
Dr. med. Claudia Cavelti-Weder, 1978, Postdoctoral Fellow am Joslin Diabetes Center in Boston. Projekt: Erlangung eines Master of Public Health. Gastinstitut: Harvard School of Public Health, Boston, USA, 1.7.2011–30.8.2013.

Zusammen mit dem Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen. Dem Stiftungsrat, unseren Stipendiatinnen und Stipendiaten und den medizinischen Fakultäten danken wir herzlich für die jederzeit sehr angenehme Zusammenarbeit.

DER CLOËTTA-PREIS 2013
WIRD VERLIEHEN

DEN HERREN PROFESSOREN DOKTOREN

ANDREAS PAPASSOTIROPOULOS

GEBOREN 1970 IN ATHEN
PROFESSOR FÜR MOLEKULARE NEUROWISSENSCHAFTEN
AN DER UNIVERSITÄT BASEL

UND

DOMINIQUE J.-F. DE QUERVAIN

GEBOREN 1968 IN BERN
PROFESSOR FÜR KOGNITIVE NEUROWISSENSCHAFTEN
AN DER UNIVERSITÄT BASEL

FÜR IHRE HERAUSRAGENDEN FORSCHUNGSARBEITEN
AUF DEM GEBIET DER ERFORSCHUNG DER NEUROBIOLOGISCHEN
UND MOLEKULAREN MECHANISMEN DES
MENSCHLICHEN GEDÄCHTNISSES.

BASEL, 6. DEZEMBER 2013

FÜR DEN STIFTUNGSRAT:

DER PRÄSIDENT

DER VIZEPRÄSIDENT

EIN MITGLIED

BIOGRAPHY

Prof. Dr. Andreas Papassotiropoulos

Andreas Papassotiropoulos has since 2007 been Professor of Molecular Neuroscience at the University of Basel. Born in 1970 in Athens he studied medicine in Bonn and received his MD in 1996. Stations of his career included the University Hospital in Bonn, the University of Zurich, as well as research visits to the USA, including the National Institute on Aging. He received his medical specialist certification as a Psychiatrist and Psychotherapist in 2001. In 2003 he received a research professorship from the Swiss National Science Foundation. His special areas of expertise include the investigation of the molecular basis of human memory and the development of improved therapies in relation to memory capacity.

Prof. Dr. Dominique J.-F. de Quervain

Dominique de Quervain has since 2009 been Professor of Cognitive Neuroscience at the University of Basel. Born in 1968 in Bern he studied medicine in Bern and received his MD in 1998. In 1997 he worked as a research fellow at the Center for the Neurobiology of Learning and Memory at the University of California in Irvine. Further stations of his career included the University Psychiatric Clinic Basel and the University of Zürich. In 2005 he received a research professorship from the Swiss National Science Foundation. His special areas of expertise include the effects of stress hormones on memory as well as the molecular basis, functional neuroimaging and the pharmacology of learning and memory process.

SELECTED PUBLICATIONS

de Quervain, D.J., Roozendaal, B. & McGaugh, J.L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. ***Nature*** 394, 787–90.

Papassotiropoulos, A., Stephan. D.A., Huentelman, M.J., Hoerndli, F.J., Craig, D.W., Pearson, J.V., Huynh, K.D., Brunner, F., Corneveaux, J., Osborne, D., Wollmer, M.A., Aerni, A., Coluccia, D., Hänggi, J., Mondadori, C.A., Buchmann, A., Reiman, E.M., Caselli, R.J., Henke, K. & de Quervain, D.J.F. (2006). Common *KIBRA* alleles are associated with human memory performance. ***Science*** 314(5798), 475–478.

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Papassotiropoulos, A., Gerhards, C., Heck, A., Ackermann, S., Aerni, A., Schicktanz, N., Auschra, B., Demougin, P., Mumme, E., Elbert, T., Ertl, V., Gschwind, L., Hanser, E., Huynh, K.D., Jessen, F., Kolassa, I.T., Milnik, A., Paganetti, P., Spalek, S., Vogler, C., Muhs, A., Pfeifer, A. & de Quervain, D.J.F. (2013). Human genome-guided identification of memory-modulating drugs. ***Proc Natl Acad Sci U S A,*** in press.

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Rasch, B., Spalek, K., Buholzer, S., Lüchinger, R., Bösiger, P., Papassotiropoulos, A. & de Quervain, D.J.F. (2009). A functional genetic variation of the noradrenergic system is related to differential amygdala activation during encoding of emotional memories. ***Proc Natl Acad Sci U S A*** 106(45), 19191–19196.

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Papassotiropoulos, A. & de Quervain, D.J.F. (2011). Genetics of human episodic memory: Dealing with complexity. ***Trends in Cognitive Sciences,***15(9), 381–387.

GENETICS OF HUMAN MEMORY: FROM GENE HUNTING TO DRUG DISCOVERY

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Abstract

Memory is a fascinating capability that allows us to store and recall events that uniquely define our lives. Memory also allows us to learn from others – a prerequisite for the development and transmission of human cultures. The relevance of memory becomes evident in conditions where memory functions are disturbed as, for example, in dementia. Here we argue that the development and combination of high-throughput human genetic methods, of elaborated statistical approaches and of sophisticated methods to quantify memory at the neural systems level will facilitate the identification of novel memory-related genes in humans. Ultimately, a crosstalk between behavioral genetic studies and investigation of causality by molecular genetic studies will pave the way towards the identification of biologically important molecules and the development of novel drugs.

Heritability of episodic memory as a prerequisite for genetic studies

During the last 4 decades animal studies in both invertebrates and vertebrates have identified genes and signaling molecules important for memory[1-5]. From this work it appears that many of the memory-related molecular mechanisms are conserved across species. However, it has been largely unknown whether these molecular pathways are also involved in human memory. The major reason for the lack of translation of the animal findings to humans is that pharmacological manipulation of many of these signaling molecules in humans is not feasible either due to safety issues or lack of pharmacologic specificity. Recent advances in the identification of genetic variants in the human genome opened, however, new avenues for the examination of complex phenotypes such as human memory. One of the major neurocognitive systems that enables conscious recollection of past experiences (e.g., autobiographical episodes, learned material) along with their spatial and temporal contexts is termed episodic memory[6] (see Glossary). From a genetic standpoint, episodic memory can be defined as a genetically complex behavioral trait with substantial heritability estimates (i.e., genetic factors account for a significant proportion of this phenotype's variance). Several twin studies report heritability values between 30 % and 60 %[7-13], indicating that naturally occurring genetic variations have an important impact on this cognitive ability. The majority of these studies treat episodic memory as a single, unified construct without breaking it down in its underlying phenotypic structure, which is characterized, for example, by temporally distinct phases as assessed by short-delay recall and long-delay recall. However, recent empiric evidence from twin studies[14] revealed both overlapping and distinct genetic influences on these temporal components of episodic memory. In brief, twin studies in non-clinical populations clearly demonstrate the genome's importance for this neurocognitive trait. The significant proportion of phenotypic variability in episodic memory that is attributable to heritable factors is a prerequisite and a starting point for targeted genetic studies aimed at identifying specific molecules and pathways thereof related to specific components of human episodic memory. Additional features of episodic memory, which render it suitable for human genetic analysis include:

- Reliable and valid phenotypic assessment: Episodic memory performance can be quantified by using reliable and valid instruments. Episodic memory is not a single phenotype, but instead may show distinct molecular profiles, depending on the specific episodic memory task (e.g., word list vs. story recall).
- Control for episodic memory-unrelated phenotypes: Factors such as attention, concentration, and motivation may influence episodic memory performance and may bias genetic association findings. Controlling for episodic memory-unrelated phenotypes is therefore crucial.
- Specific neural correlates: Episodic memory has well definable and well quantifiable neural correlates (e.g., memory-related activity of the hippocampus and parahippocampal gyrus). This allows for further corroboration of genetic association findings at the neural systems level.
- Independent replication: Regardless of the statistical models used and however simple or complicated they might be, successful gene identification stands and falls with independent replication of the gene-phenotype associations. This is particularly important in the era of genome-wide studies (GWAS), which screen for association between heritable traits and millions of genetic variants distributed over the entire genome, thereby introducing a multiple testing burden.

Genetic association studies with candidate genes

Whenever sufficient knowledge about the biological mechanisms underlying the physiology (and in case of disease, the pathophysiology) of a certain trait exists, candidate gene association studies, which assess the correlation between one or more variants of a biologically plausible gene (or a set of genes) with the phenotype, may be readily implemented. In the case of episodic memory, sufficient biological knowledge does exist. A number of animal studies have identified genes and signaling molecules important for memory, including protein kinases and phosphatases, transcription factors, growth factors, and receptor complexes[1-5]. These studies suggest that molecules related to learning-related synaptic plasticity, long-term potentiation (LTP), long-term depression (LTD), and activity of such brain structures as the hippocampus, parahippocampal gyrus, and the amygdala might represent ideal biological candidates for

genetic association studies. Indeed, in 2003 two articles supported the notion that the candidate gene approach is promising by showing that functional gene variants, so called single nucleotide polymorphisms (SNPs, see Glossary), in the genes encoding the 5-hydroxytryptamine (serotonin) receptor 2A (*HTR2A*) and the brain-derived neurotrophic factor (*BDNF*) are associated with episodic memory performance[15, 16]. Both molecules are highly expressed in the hippocampus and the cerebral cortex and have been implicated in animal learning and memory[17-19]. In humans, a common *HTR2A* SNP predicts an amino acid substitution (His to Tyr) at residue 452 (H452Y). Compared with carriers of the common His/His variant, heterozygous (His/Tyr) carriers show a blunted receptor response upon pharmacological stimulation with serotonin[20, 21] and poorer episodic memory performance in verbal and figural tasks[15]. *BDNF* harbors a SNP which is located in the 5′ pro-BDNF sequence and results in a Valine to Methionine substitution at codon 66. The *Met* allele is related to deficits in the cellular distribution and regulated secretion of BDNF and to poorer episodic memory performance[22]. The demonstration of successful identification of episodic memory-related molecules through the candidate gene approach prompted subsequent studies, which reported on such additional genes related to this cognitive capacity. Although the majority of these studies remain to be independently replicated, they do suggest that focusing on pre-existing and well-established biological information may lead to the identification of genes related to episodic memory in humans.

Genome-wide association studies (GWAS)

While pre-existing biological information clearly facilitates the search for biologically meaningful candidates, it may on the other hand introduce a severe bias towards readily accessible molecular pathways and it definitely limits the potential of genetic association studies to identify novel genes and molecular pathways. Recent advances in the development of high-density genotyping platforms and analytical software now allow for high-resolution GWAS, which screen for association between heritable traits and millions of genetic variants distributed over the entire genome. This dense screening feature renders GWAS particularly useful in discovering novel molecular pathways of genetically complex traits.

The first GWAS on episodic memory identified *KIBRA* and *CLSTN2* as episodic memory-related genes[23]. Replication studies in European and Asian populations further supported the role of *KIBRA* in episodic memory (e.g.,[24-27]). Importantly, a study in two large Scottish samples suggested that *KIBRA* is related to processes specific to the conscious recall of item-based material, possibly reflecting hippocampal processing[24]. This high degree of specificity underscores the importance of precise phenotypic assessment in behavioral genetic research, including replication studies. Subsequent GWAS in healthy participants supported the role of additional genes such as *CAMTA1*[28] and *NRXN1*[29] in episodic memory performance by using a variety of neuropsychological measurements. It is important to stress that the genes identified through genome-wide screening are involved in memory-related molecular pathways such as protein phosphorylation, calcium-responsive transcriptional activation, and – in general – synaptic plasticity. Nevertheless, it is highly unlikely that most of these genes would have been selected a *priori* in a candidate gene setting, simply because very little was known regarding the biological relevance of these genes prior to their identification in the course of the GWAS. This demonstrates the substantial potential of this approach for the identification of novel genes and pathways related to human episodic memory. Our knowledge about the molecular underpinnings of this trait has already increased and it will undoubtedly continue to increase as larger and denser GWAS, utilizing refined analytical methodology, are expected in the near future.

Genetic complexity

GWAS may powerfully identify components of the genetic basis of complex, multigenic traits. In the past few years, GWAS using hundreds of thousands and even millions of polymorphic markers, mainly SNPs, in samples ranging from a few hundreds to several thousands of individuals have led and still lead to the identification of numerous susceptibility genes and trait-related genomic variants. However, despite this extensive use of genetic and analytical force, which has undoubtedly proven successful, a major portion of the heritability of complex traits still remains unexplained, a phenomenon commonly termed «missing heritability»[30].

Gene-gene interactions

In addition to epigenetic factors, causal but non-examined rare variants, and environmental influences, the negligence of analytical approaches accounting for gene-gene interaction effects, such as statistical epistasis, may partly explain the phenomenon of «missing heritability»[31]. Indeed, despite the obvious conception that the analysis of genetically complex traits should account for the underlying biological and statistical complexity, the vast majority of large-scale genetic association studies to date are restricted to the use of single marker statistics. Clearly, this approach does not fully account for the polygenic nature of the phenotype under study and erroneously implies that the impact of genetic variation is due to independently acting effects.

The above also holds true for the study of the genetics of episodic memory. Although the large-scale analysis of statistical epistasis related to complex traits has proven feasible[32], only few studies have addressed epistatic effects of a limited number of genetic variants on cognitive functions[33-36]. In the light of the complex polygenic nature of episodic memory, studies accounting for the statistical interaction between few (e.g., two) genetic variants should be regarded as proof-of-principle studies and as a starting point for more complex approaches. However, studies involving comprehensive sets of genetic variants and addressing interaction (e.g., epistatic) effects on human memory are still lacking. The concept of statistical epistasis was defined about a century ago and deals with the statistical deviation from additive interaction effects between genetic markers[37]. Per definition, the inclusion of such statistical interaction terms as epistasis exponentially increases the number of statistical tests performed. For example, a two-way interaction analysis between 1000 single markers requires the performance of 499 500 tests. Some strategies attempting to limit the number of necessary tests in analyses of epistasis employ a stepwise procedure by including only those interaction terms, for which the corresponding marker showed a significant main effect in the first step single-marker analysis. However, this approach is arbitrary as there is no biological rationale for considering only markers with significant main effects. Indeed, a recently published report of an exhaustive genome-wide analysis showed that significant epistatic interactions would have been missed if SNPs that did not display any main effect had

been excluded *a priori*[38]. It remains to be shown whether these exhaustive approaches will prove feasible and successful in the study of the complex genetic architecture of episodic memory.

Gene clusters

Rather than computing complex gene-gene interactions, another approach to capture the interplay between genetic variants and its impact on episodic memory focuses on the computation of compound gene and SNP clusters based on multi-locus analyses. For example, a permutation-based method, termed set association, evaluates sets of polymorphic markers and provides a cluster of significant alleles and genotypes with a single test statistic. Importantly, such compound analyses defining gene clusters can be used for the calculation of aggregate, individual genetic scores, which principally reflect a person's number of trait-associated genetic variants weighted by the effect size of each variant. With regard to episodic memory, such approaches have proven feasible[39] and extendable to conditions of pathological cognition[40]. These multi-locus methods represent an extension of the candidate gene approach and deal with sets of genes in biologically meaningful candidate pathways. A pre-selection of the human homologues of 47 genes with well-established molecular and biological functions in synaptic plasticity and animal memory led to the identification of a 7-gene-cluster associated with episodic memory[39]. This gene cluster represents such important memory-related molecules as adenylyl cyclases, kinases, and glutamate receptors. An aggregate, individual gene score based on the 7-gene-cluster was also associated with activations in memory-related brain regions, such as the hippocampus and parahipocampal gyrus (Figure 1). The computation of aggregate genetic scores based on genetic clusters has hitherto relied on pre-existing information (i.e., a candidate pathway approach). Recently, similar gene clustering methods have been used for the calculation of genetic risk profiles by utilizing GWAS data[41]. Most probably, capitalizing on a combination of GWAS data and gene clustering methods will also facilitate the unbiased identification of novel gene clusters related to episodic memory capacity.

(a)

GRIN1	GRINA	CAMK2A	PRKACA	PRKAR1A	PPP3CB	ADCY8
GRIN2A	GRM1	CAMK2B	PRKACB	PRKAR2B	PPP3CC	CREB1
GRIN2B	GRM3	CAMK2D	PRKACG	MAPK1	PPP1CA	CREB3
GRIN2C	GRM4	CAMK2G	PRKCD	MAPK3	PPP1CB	CREBBP
GRIN2D	GRM5	PRKCA	PRKCE	FYN	PPP1CC	NCAM1
GRIN3A	GRIA1	PRKCB1	PRKCH	CALM2	ADCY1	
GRIN3B	GRIA4	PRKCG	PRKAG1	PPP3CA	ADCY2	

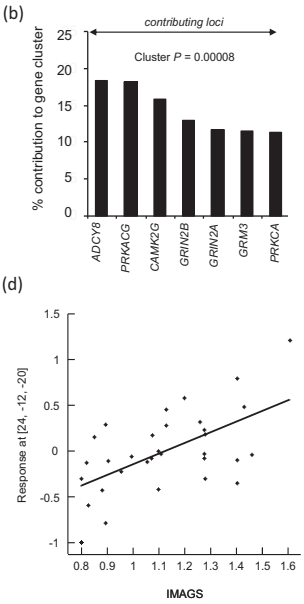

Figure 1. *Gene score related to human episodic memory and memory-related brain activity. (a) Squares represent a selection of the human homologues of 47 genes with well-established molecular and biological functions in synaptic plasticity and/or animal memory. Squares in red represent the 7 genes for which significant association of genetic variations with human episodic memory was found. (b) The seven-SNP cluster was used for the calculation of an individual›s memory-related genetic score, termed individual memory-associated genetic score (IMAGS). (c) Regression analysis revealed a significant positive correlation between the IMAGS and learning-induced brain activations in the medial temporal lobe (MTL), including the hippocampus and parahippocampal gyrus. (d) Scatter plot illustrating the positive correlations between IMAGS and learning-induced brain activations in the hippocampus at coordinate position[24, -12, -20]. Adapted from[39].*

The quest for the ideal statistical methodology

We believe that it is impossible to predict which statistical and bioinformatics approaches will ideally explain the relationship between genetic and phenotypic variability of such complex traits as episodic memory. It will be most probably a combination of several approaches specific to distinct memory-related phenotypes. The obvious genetic complexity of episodic memory along with studies showing the importance of statisti-

cal methods accounting for gene-gene interactions supports the notion that rare combinations of common variants significantly account for this trait's variability and heritability. Therefore, the study of the genetic architecture of episodic memory will require a statistical and systems biology framework that accounts for the complexity of the interacting functional molecular networks. The current approaches (e.g., set-association[42], set-based tests[43], multifactor dimensionality reduction[44], gene set enrichment analysis[45], to name just a few) are clearly a very good start. However, as more and more methods will become available, study designs based on multidisciplinary research frameworks and focusing on replication of the identified complex genetic structures will prove invaluable for the robust and reliable discovery of parts of the genetic underpinnings of episodic memory.

Phenotypic complexity

Episodic memory refers to memory for past experiences (e.g., autobiographical episodes, learned material), which includes information about the content of the experience and the spatial and temporal context in which it occurred[46, 47]. It is important to realize that in terms of neurobiological underpinnings, episodic memory performance may be subserved by distinct molecular profiles, depending on the specific episodic memory task used for quantifying performance. For example, the BDNF Val66Met polymorphism has been shown to be associated with delayed recall from stories of the Wechsler Memory Scale, revised version, but not with delayed recall of a word list taken from the California Verbal Learning Test[16] – yet both tasks are referred to as episodic memory tasks. Furthermore, it is well known that emotionally arousing information is better stored into memory than neutral information and that this phenomenon depends on the activation of noradrenergic transmission[48, 49]. Consequently, it has been shown that a functional deletion variant of *ADRA2B*, the gene encoding the α2b-adrenergic receptor, is related to differential episodic memory performance for emotionally arousing pictures, but not for neutral pictures[50]. Furthermore, it is important to note that several factors, which are not considered to belong to episodic memory, such as motivation, attention or concentration can have a large impact on performance in episodic memory tasks. Thus, in behavioral

genetic studies on episodic memory it is crucial to control for such unspecific factors.
The phenotypic complexity with regard to episodic memory not only has important and obvious implications for replication studies[24], but also for meta- and mega-analyses (i.e., the use of raw data from individual subjects across different studies): By combining several similar, but not identical, episodic memory phenotypes, genetic studies may identify statistically robust associations pointing to common denominators of these phenotypes, but are likely to miss molecules specifically related to a distinct phenotype with distinct neurobiological features.

Imaging genetics

Besides the importance of replicating genetic association studies on episodic memory it is important to also consider additional methods for further corroboration and better understanding of the behavioral genetics findings. In the recent few years, brain-imaging techniques, in particular functional Magnetic Resonance Imaging (fMRI), have become increasingly popular for this purpose[23, 51-53]. The rationale for combining behavioral genetic and neuroimaging methods is to validate and extend purely behavioral genetic studies by providing insight into the genetic differences in memory processes at the level of neural circuits[54]. So far, the majority of imaging genetic studies has looked at single markers in relation to brain activation differences. However, considering the genetic – and phenotypic complexity of human episodic memory, another promising approach involves studying specific genetic networks (comprising multiple markers in different genes) related to a certain episodic memory phenotype by investigating compound genetic scores in relation to brain activity[39] (Figure 1).
The interpretation of genotype-dependent differences in brain activity critically depends on the fMRI study design and the behavioral findings of the fMRI sample. Whenever significant performance differences across genotype groups exist, a possible outcome is higher activity in memory-related brain regions in the genotype group that shows higher memory performance[55]. In the case genotype groups of the fMRI sample have been matched for performance, brain activity increases for the genotype group with low memory performance in the unmatched population can be

interpreted as compensatory activity to achieve the same level of performance as the genotype group with high memory performance[23]. Interpretation becomes difficult if the fMRI study reveals genotype-dependent activity differences despite non-significant differences in memory performance in genotype groups unmatched for performance. This situation is common, because the number of subjects used in imaging genetic studies reporting significant genotype-dependent differences in brain activity typically lay between 20 and 60 subjects, whereas behavioral genetics studies usually used hundreds or thousands of subjects to consistently produce significant results[54]. A possible explanation for this observation is that neural activity is more proximate to the direct effects of functional genetic polymorphisms on gene products and their function, and might therefore be more sensitive in estimating genotype-dependent differences in mental processing[54, 56, 57]. Nevertheless, genotype-dependent differences in brain activity that do not translate to significant differences in behavior should be interpreted with caution.

From gene hunting to drug discovery

As highlighted above, the recent advances in human genetics have led to an unprecedented rate of discovery of genes related to complex human disease, including neuropsychiatric disorders[58-60]. The human genome-based gain of knowledge is certainly expected to have a large impact on drug discovery in complex human disease[61-63]. It is, however, still not clear to what extent this knowledge can be used as a starting point for the identification of druggable molecular pathways of complex traits, including mental disorders. Very recently, we focused on emotionally aversive episodic memory – a trait central to anxiety disorders such as posttraumatic stress disorder (PTSD). Strong memory for emotionally arousing events can be seen as a primarily adaptive phenomenon, which helps us to remember vital information (e.g. dangerous situations). In case of an extremely aversive event, however, this mechanism can also lead to intrusive and persistent traumatic memories, thereby contributing to the development and symptoms of PTSD. Symptoms related to aversive memory include intrusive daytime recollections, traumatic nightmares and flashbacks in which components of the event are relived. Aversive memory is a genetically complex trait as shown both in healthy subjects

and in traumatized individuals[50, 64]. Furthermore, we recently reported evidence suggesting a genetic link between the predisposition to build strong aversive memories and the risk for PTSD[64].
Based on these observations, we decided to perform a multinational collaborative study, which included assessment of aversive memory and a gene-set analysis in healthy individuals. We identified 20 potential drug target genes in 2 genome-wide corrected gene sets, the neuroactive ligand-receptor interaction and the long-term depression gene set. In a subsequent double-blind, placebo-controlled study in healthy volunteers we aimed at providing a proof-of-concept for the genome-guided identification of memory modulating compounds. Pharmacological intervention at the neuroactive ligand-receptor interaction gene set led to significant reduction of aversive memory. This recent study demonstrated that genome information, along with appropriate data mining methodology, can be used as a starting point for the identification of memory-modulating compounds[65].

Concluding remarks

As with any genetically complex trait, neuroscientists focusing on the study of the genetic underpinnings of episodic memory have to deal with manifold complexity levels. First, the trait (i.e., episodic memory) *per se* represents an assembly of phenotypes with overlapping, but also partially distinct molecular profiles. Secondly, complexity at the genetic level is not only related to the polygenic nature of the trait itself, but it also reflects the complexity of the human genome, which exerts its influence on the trait not only through simple, linear gene effects, but also through gene-gene interactions, gene-environment interactions, and epigenetic mechanisms. Finally, the relation between genetic and phenotypic variability is not expected to follow simple and general rules applicable to every memory-related phenotype.
Despite this obvious complexity, empirical evidence supports the notion that behavioral genetic studies of episodic memory successfully identify trait-associated molecules and pathways. As new technological and analytical approaches – both at the genetic and the phenotypic level – emerge, two simple and important pillars of reliable genetic research must not be forgotten: Firstly, regardless of the statistical models used and how-

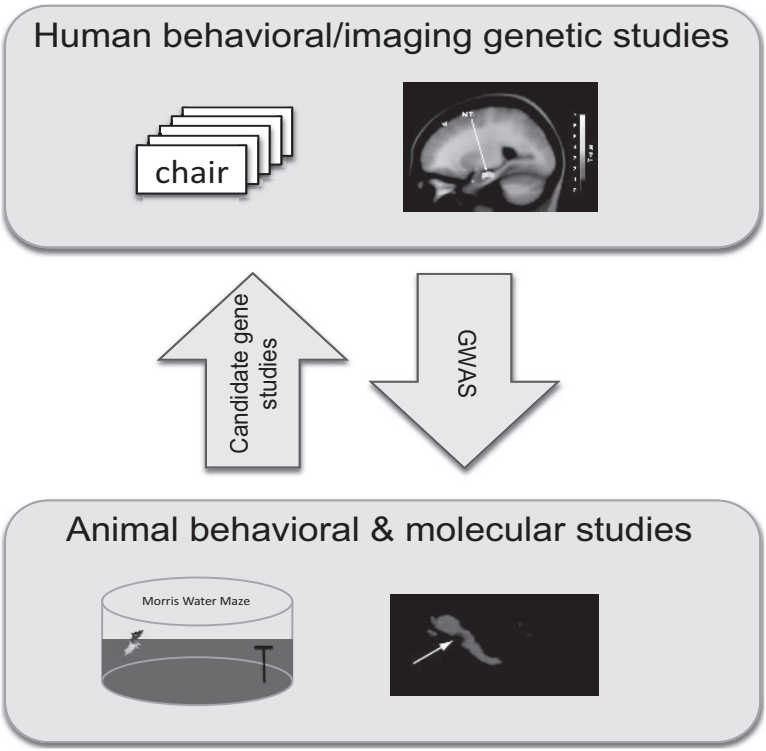

Figure 2. *Crosstalk between behavioral/imaging genetic studies in humans, and behavioral and molecular genetic studies in animals. Human candidate gene studies depend on preexisting information, which mostly origins from animal and molecular studies. Genome-wide association studies (GWAS) often identify genes, for which the function is not known or poorly understood. In such cases, behavioral and molecular genetic studies in animals may be useful to learn more about the causal role and the function of the gene. Taken from*[66].

ever simple or complicated they might be, successful gene identification stands and falls with independent replication of the gene-phenotype associations. Secondly, given the correlative nature of behavioral genetic research, genetic findings must be corroborated through implementation of additional phenotypic assessment and methods. Whereas fMRI is certainly a powerful tool to gain insight into the genetic differences in mem-

ory processes at the level of neural circuits, it is important to note that imaging genetic studies are also correlational in nature and do not allow causal interpretations. Methods, which allow researchers to investigate the causal role of a certain gene or genetic variant include studies in genetically modified animals and studies aiming at intervening at the level of gene products. Such studies are especially important to gain more knowledge about genes identified in GWAS, for which the function is not known or poorly understood (Figure 2). This crosstalk between genetic association and investigation of causality will ultimately pave the way towards the identification of biologically important – and druggable – genes and molecular pathways related to human episodic memory.

Glossary

Allele: one of two or more forms of a gene, located on a specific position on a chromosome.

Complex trait: a quantifiable property of an organism influenced by both genetic and environmental factors as well as interactions between them.

Epigenetics: research field that investigates potentially heritable changes in gene expression caused by mechanisms other than changes in DNA sequence.

Episodic memory: a memory system that enables conscious recollection of past experiences (e.g., autobiographical episodes, learned material) along with their spatial and temporal contexts.

Missing heritability: describes the fact that despite the success of large and dense genome-wide scans in the discovery of trait-associated genetic variants, a large portion of the heritability of complex traits still remains unexplained.

Phenotype: physical appearance of an organism with respect to a trait (e.g., blue eye color).

Polymorphism: in genetics, a difference in DNA sequence among individuals. A common form of a genetic polymorphism is a single nucleotide polymorphism (SNP), which occurs when a nucleotide – A, T, C, or G – differs between individuals. The human genome contains millions of SNPs.

Statistical epistasis: a concept defined about a century ago and dealing with the statistical deviation from additive interaction effects between two or more genetic polymorphisms.

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