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Genetic influences on emotion/cognition interactions – from synaptic regulation to individual differences in working memory for emotional faces

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(Dipl. Biol.)

This thesis is submitted in part fulfilment of the degree of Doctor of Philosophy, completed at the Wolfson Centre for Clinical and Cognitive Neuroscience, School of Psychology, Bangor University, Bangor, LL57 2AS, UK.

Table of Contents

Abstract

Individual differences in human behaviours including cognitive functions reflect the integration of genetic, epigenetic and environmental influences that regulate adaptation mechanisms across functional levels. How these different influences are integrated to regulate adaptation mechanisms across functional levels is a key question of contemporary research. One novel technique to investigate the integration of genetic and environmental influences at the level of neural networks and its relation to behaviour is genetic neuroimaging. We used this technique to investigate whether individual genetic differences influence the individual performance and task-related brain activity in working memory for emotional faces. Results revealed effects of variability in the gene for the synaptic protein dysbindin-1 on working memory performance and its neural correlates that depended on the type of emotional face expression. This suggests that genetic influences are integrated with environmentally-driven stimuli at the neural network level to regulate the behavioural response.

Interindividual differences are also reflected in the degree of impairment in cognitive functions such as working memory in patients with schizophrenia. We were interested in the biological basis of relatively preserved cognitive functions in a subgroup of the patients with schizophrenia. Using fMRI we compared brain activity related to accurate WM performance in patients with matched control participants. Patients and controls showed activity increases and decreases in different brain regions. This indicates that patients with preserved WM function may compensate insufficient support from dysfunctional regions through hyperactivation in less affected regions.

Working memory for emotional faces as an endophenotype for schizophrenia

a) What is working memory?

Most cognitive functions involve working memory (WM), e.g. comprehension, imagination, planning, thinking and coordination of actions. Cowan (Cowan, et al., 2005), defined WM as "the set of mental processes holding limited information in a temporarily accessible state in service of cognition". WM depends on short-term plasticity of neural networks[1] for the transient (from hundreds of milliseconds to seconds) maintenance (i.e. accessibility) and transformation of neural representations (that represent information with multiple continuous and discrete dimensions from low to high levels[2]) that were induced by internally or externally-generated signals. The view of WM as a function for short-term maintenance and active processing of neural representations based on multi-unit system was introduced by Baddeley (Baddeley & Hitch, 1974). However in this model maintenance relies on various modality-specific units as well as on a processing-specific unit (Baddeley, 1992). Such a separation of executive from storage processes during WM tasks has been questioned by fMRI studies because a single region like the DLPFC can be engaged in both, maintenance and transformation processes (J. D. Cohen, et al., 1997; D'Esposito, Postle, & Rypma, 2000) as well as several prefrontal and parietal regions can interact during transformations (Wager & Smith, 2003). The neural networks of working memory comprise areas in sensory, somatosensory and often parietal, frontal and temporal cortex (D. Linden, 2007). The recruitment and the degree of engagement of these areas depend on the specific combination of task characteristics such as the capacity demand (e.g. load, delay length, interference, task

[1] Short-term neural network plasticity – the neuronal activity-dependent adaptability of neural networks based on rapidly elicited, transient adaptations of molecular, neuronal and neural system functions

[2] Processing level low if selective for, e.g. contrast, spatial orientation, intensity or high level if selective for, e.g. object categories; continuous, e.g. intensity or discrete, e.g. object identity

complexity), sensory system(s) involved (e.g., visual, auditory), domain(s) of interest (time, location, object), object category(ies) (e.g., faces), abstraction level(s) of the representation (symbolic, non-symbolic), delay, time course of the task and type of process (maintenance, transformation) (D. E. Linden, et al., 2003; Mohr, Goebel, & Linden, 2006; Mohr & Linden, 2005; Munk, et al., 2002; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). Coding through both highly selective (e.g. location-WM) as well as flexible (e.g. switching from object-WM to location-WM) frontal neurons could explain dissociation and overlap of neural activity within frontal regions across various cognitive tasks (Duncan & Owen, 2000). Overlap has been observed for some regions being active during perceptual processing, transient maintenance and recognition phase with other regions being only involved during a single phase of delayed match-to-sample tasks (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002). Task-related activity was found to be increased for correct compared to incorrect responses (Pessoa, et al., 2002). In particular during the maintenance phase a correlation was observed between the fMRI signal amplitude in a prefrontal-parietal network and the task performance (Pessoa, et al., 2002). The relation between working memory performance and cortical activity depends on the brain region and for the prefrontal cortex is best modelled by an inverted-U function (J. H. Callicott, et al., 1999).

Together these findings suggest that the specific task requirements during WM are reflected in the spatial-temporal pattern of brain activity. However, how interactions between molecular, cellular and network plasticity mechanisms drive these changes and thus enable short-term plasticity in WM remains largely elusive. Short-term changes (as opposed to long-lasting changes) in whole-brain network activity may emerge form short-lasting changes in functional connectivity that rely on short-term changes in the activity of individual circuits, which are based on transient activity changes in individual neurons that depend on current or recent changes in their intercellular communication, their subcellular and molecular components (intracellular environment) as well as their extracellular environment. Currently it

remains an unsolved question how temporal-spatial changes in brain activity are regulated to dynamically integrate neural representations over very short time intervals. Information is sparse regarding what short-term plasticity mechanisms at each of these functional levels are involved and how they interact in the regulation of short-lasting changes to integrate neural representations across short time intervals. Mechanisms for short-term plasticity may be based on the same principles across functional levels because of their functional similarities although they are realized by different structures or functional elements (Maex & Steuber, 2009). One example is spatial-temporal switching between multiple discrete (stable) activity states. Discrete states of amplitudes or frequencies can be observed in cortical networks (Tsodyks, Kenet, Grinvald, & Arieli, 1999) and individual neurons (Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002). From the temporal relation between these discrete states emerge other discrete states, e.g. synchronization/desynchronization, synaptic facilitation/ depression, inhibition/ excitation. At the molecular level discrete activity states of signalling, receptor or channel proteins also exist mediated e.g. through phosphorylation/dephosphorylation. The spatial-temporal coordination between multiple stable states within and across functional levels could play a role in the integration of neural representations across short time intervals. For example transient synaptic facilitation mediated by increased intracellular Ca^{2+}-concentrations of neurons that were activated during encoding of the representation to transiently tag those neurons to facilitate their reactivation during retrieval has been proposed as a mechanism for short-term plasticity of WM (Mongillo, Barak, & Tsodyks, 2008). Activation-induced transient changes in synaptic strength that facilitate neuronal reactivation thus switching between synaptic state- and neuronal activity state-dependent representations could maintain neural representations across short-delays. Indeed it has been shown that the population average responses of stimulus-selective neurons in the inferior temporal cortex differ between match and non-match

conditions during delayed match-to-sample tasks (Sugase-Miyamoto, Liu, Wiener, Optican, & Richmond, 2008).

Short-term synaptic facilitation/ depression could also be involved in the regulation of the temporal relation between discrete frequencies generated by neurons or neural networks during WM tasks. For example the synchronization of discharges between interacting neurons could depend on short-term changes in synaptic strength mediated through facilitation/ depression (Fujisawa, Amarasingham, Harrison, & Buzsaki, 2008), or alternatively through short-lasting changes of membrane conductances (Marder, Abbott, Turrigiano, Liu, & Golowasch, 1996). The temporal relation between discrete frequencies produced by large networks of active neurons has been shown to dissociate between processes of information selection and maintenance as well as their influence on WM capacity (Sauseng, et al., 2009).

These short-term changes at the neural network and neuronal level are mediated by short-lasting molecular changes, in particular the phosphatase-kinase ratio depending on intracellular Ca^{2+}-concentration could be critical for WM function (Dash, Moore, Kobori, & Runyan, 2007). The Ca^{2+}-dependent regulation of signalling proteins involved in synaptic vesicle exocytosis (R. C. Lin & Scheller, 2000), permeability of ion-channels (Levitan, 2006) or receptor sensitivity (X. Y. Liu, et al., 2009) are examples for molecular short-term modification of synapses.

Future attempts to identify the neural basis of WM need to investigate interactions between short-term plasticity mechanisms across molecular, neuronal and neural network levels in tight combination with studies that address each level separately. Another interesting question is how genetic variability that affects short-term plasticity contributes to individual differences in WM capacity.

b) What is schizophrenia?

Schizophrenia is a multifactorial complex psychiatric disorder that is characterized by pronounced clinical, biological and etiological heterogeneity (Tandon, Nasrallah, & Keshavan, 2009). It occurs with a lifetime risk average of about 0.7 percent (Saha, Chant, Welham, & McGrath, 2005) that varies with the degree of genetic predisposition (Allen, et al., 2008; Gottesman, II, McGuffin, & Farmer, 1987; Heston, 1966; Kendler, et al., 1993a) gender (Aleman, Kahn, & Selten, 2003; McGrath, et al., 2004), urbanicity (G. Lewis, David, Andreasson, & Allebeck, 1992; Pedersen & Mortensen, 2001), migration (Cantor-Graae & Selten, 2005; Malzberg, 1964), prenatal infections (Penner & Brown, 2007), obstetrical complications (Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Geddes & Lawrie, 1995; Geddes, et al., 1999), drug abuse (Semple, McIntosh, & Lawrie, 2005) and parental age (Wohl & Gorwood, 2007). However how these genetic and environmental risk modulating factors interact and what neurobiological processes mediate their individual effects and interactions is currently unknown (van Os & Marcelis, 1998; van Os, Rutten, & Poulton, 2008). Until these neurobiological processes have been identified it will be impossible to prove that any of these factors influence the risk of schizophrenia. The identification of risk factors also depends on a second question, the very definition of schizophrenia itself. Defining schizophrenia has been proven difficult because of the relative symptom- and treatment-unspecificity with respect to other psychiatric disorders and lac of diagnostically-valid markers (including genetic, patho-physiological/psychological markers) (Moller, 2008). Some of the symptoms observed in patients with schizophrenia are also seen in patients diagnosed with other psychiatric disorders, e.g., personality disorders (Siever & Davis, 2004), affective disorders (Angst, 2002; Taylor & Amir, 1994) and autism (Esterberg, Trotman, Brasfield, Compton, & Walker, 2008). This suggest the existence of some continuous transitions between disorders and disorder categories (H. Verdoux & van Os, 2002) as well as some overlap in neuropathology (O'Dushlaine, et al., 2010). Interestingly personality disorders are

more frequent in relatives of patients with schizophrenia (Kendler, et al., 1993b; Maier, Lichtermann, Minges, & Heun, 1994). Characteristic symptoms according to DSM-IV (American Psychiatric Association, 2000) include delusions, hallucinations, disorganized language and behaviour or catatonic behaviour, negative symptoms (i.e. affective flattening, alogia, or avolition). Delusions, hallucinations, catatonic and negative symptoms overlap with the characteristic symptoms according to ICD-10 (World Health Organisation, 1992) but differ for the symptoms thought echo/insertion/withdrawl/broadcasting and social and occupational dysfunction. Both systems require for the diagnosis of schizophrenia the exclusion of organic causes for symptoms and do not include the impairment of cognitive functions nor subjective experiences. The inclusion of the impairment of cognitive functions (Keefe, 2008) and subjective experiences (Raballo, Saebye, & Parnas, 2009; Sass & Parnas, 2003) as diagnostic criteria may be valuable, e.g. for early detection and treatment of the disorder as well as for the identification of pathological mechanisms and risk factors. Both classification systems differ with respect to the required number, specificity and duration of symptoms. The diagnosis depends thus critically on the applied diagnostic classification system. Such differences in the degree of diagnostic concordance between classification systems for schizophrenia, e.g. duration and exclusion/inclusion of symptoms, affect the estimation of incidence rates, prevalence, heritability and outcome (Jansson & Parnas, 2007). At present there is increasing doubt in the validity and utility of these systems for the classification of mental disorders (Craddock & Owen, 2010; Eaton, Hall, Macdonald, & McKibben, 2007; Jansson & Parnas, 2007; Moller, 2008; van Os, 2009).

The age-at-onset of schizophrenia varies with gender (Angermeyer & Kuhn, 1988) and family history of schizophrenia (Esterberg, Trotman, Holtzman, Compton, & Walker, 2010). In cases with a family history of schizophrenia no effect of gender on the age-at-onset was evident (Esterberg, et al., 2010). A younger age-at-onset has been related to an increased severity of cognitive deficits (Rajji, Ismail, & Mulsant, 2009). Course and outcome are also heterogenous

(Tandon, et al., 2009), worse course and outcome of the illness have been reported for younger age-at-onset (Hollis, 2000; Rabinowitz, Levine, & Hafner, 2006) and more severe cognitive deficits (Bowie, et al., 2008; Braw, et al., 2008). The risk for death by suicide is relatively high in patients with schizophrenia (Pompili, et al., 2007; Saha, Chant, & McGrath, 2007). Comorbity of other psychiatric disorders, drug abuse, intellectual disability and a range of medical conditions has been observed with schizophrenia (Tandon, et al., 2009). The various treatments for schizophrenia are limited by variability in individual symptomatoloy and treatment response, insufficient effectiveness, treatment resistance, significant side effects and non-compliance (De Oliveira & Juruena, 2006; Dixon, et al.; S. Lewis & Lieberman, 2008; Matheson, Green, Loo, & Carr; Tandon, et al., 2008). Complete remission from schizophrenia is relatively rare but psycho-social and vocational rehabilitation may improve prognosis (Schennach-Wolff, et al., 2009).

The prevalence and high heritability of schizophrenia in human populations despite its negative effects has led to the idea that genes conferring risk to schizophrenia could also be involved in adaptive evolution of human cognitive functions (Crespi, Summers, & Dorus, 2007). This view is supported by the finding that some of the strongest and best-replicated schizophrenia-associated genes are under recent positive selection (Crespi, et al., 2007).

Even though the diagnosis is categorical most of the current theoretical models of schizophrenia assume and experimental data support continuous structures of symptomatology, individual symptom phenotypes, pathophysiology and etiology of the disorder (Linscott & van Os). Nevertheless these quantitative structures may give rise to qualitative structures at the population level (Linscott & van Os). Research and treatment of schizophrenia could be advanced through the improvement and empirical validation of the current concepts and diagnostic systems e.g., through the integration of categorical and continuous measures covering symptomatology, pathophysiology and etiology using unbiased methods (Keshavan, Tandon, Boutros, & Nasrallah, 2008; Linscott & van Os). Furthermore

the utility of traditional subtypes of schizophrenia has been questioned because they are unstable during the course of the disorder and futile to explain the heterogeneity in clinical profile, etiology, pathophysiology, treatment response, and outcome (Tandon, et al., 2009). Instead of these traditional subtypes, the variable expression of individual symptom clusters could be used to better differentiate pathophysiological processes, risk factors, individual courses and treatment responses between patients (Tandon, et al., 2009). The decomposition of these symptom clusters in continuous measures (endophenotypes) may also reveal how risk factors affect neurobiological processes (Tandon, et al., 2009).

c) The quest for endophenotypes of schizophrenia

The concept of endophenotype was invented to decompose complex, polygenetic and heterogeneous disorders (reviewed by (I. Gottesman & Gould, 2003)). This is based on the assumption that identification of the genetic contribution to a specific feature of a disorder-related phenotype (e.g. expression level of a protein, neuropil size, ventricle size or cognitive deficit) will facilitate the association between disorder-related genotypes and phenotypes. The endophenotype was proposed to uncover functional relationships between genotype and disorder through the identification of genetically influenced modifications at various functional levels, e.g. at the molecular, cellular, neural network and behavioural level. Appropriate endophenotypic traits are more directly related to the biological effects of fewer genes, influenced by fewer factors, and less complex than their associated phenotype.

According to Gottesman and Gould (I. Gottesman & Gould, 2003) suitable endophenotypes should fulfil the following five criteria: associated with the illness at the population level, heritable, present whether or not symptoms are present, within families co-segregate with the illness and presentation in affected individuals more similar or common in non-affected relatives than in the general population.

Susceptibility to schizophrenia is suggested to be multifactorial resulting from the complex interactions between genetic, epigenetic and environmental factors, with a heritability estimate[3] of approximately 0.8 (Cardno & Gottesman, 2000; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). The polygenetic and heterogeneous inheritance of schizophrenia is reflected in the individual variation of symptom combinations, the considerable heterogeneity of disorder course, outcome as well as its symptoms. The number of susceptibility loci, the disorder risk conferred by each locus, the extent of genetic heterogeneity, and the degree of interaction of loci all remain unknown (G Kirov, O'Donovan, & Owen, 2005). However recent evidence suggest that genetic risk of schizophrenia is conferred by common alleles of moderate to small effect and rare alleles of moderate to large effects in multiple genes (H. J. Williams, Owen, & O'Donovan, 2009). Because the individual effect of most putative risk alleles is small and those alleles are common in the general population various combinations of multiple risk alleles at multiple loci interacting with one another and environmental factors may underlie the pathogenesis and explain the heterogeneity of schizophrenia. In addition rare alleles of larger effect like copy number variations may contribute to the etiology in some cases of schizophrenia (G. Kirov, et al., 2008; Walsh, et al., 2008). The investigation of such complex patterns of risk variables is still lacking because of the difficulty to model such high-dimensional data without knowledge about the functional relations between the variables. Genome Wide Association Studies (GWAS) rely on individual testing of each variability marker/ haplotype i.e. multiple testing that requires very large samples to test whether the frequencies of genetic variants differ between affected individuals and controls. The endophenotype approach instead focuses on relations between genetic variability and differences between patients and controls in disease-affected quantitative traits e.g. brain functions and structures. Understanding the impact of genetic variability on schizophrenia-

[3] Heritability – is a measure of the strength of genetic effects on a trait, most generally defined as the proportion of the phenotypic variance in a trait that is attributable to genetic effects (heritability = genetic variance/ phenotypic variance)

related alterations of brain functions and structures may help to define more homogenous clinical phenotypes to assist diagnosis and treatment selection. Quantitative endophenotypes may also replace the case-control design to enhance the power of genetic association studies. Positive, negative, disorganized and cognitive symptoms in schizophrenia can affect multiple functions, e.g. perception, locomotion, emotion, social-interaction, executive functions and memory. Repeatedly, genetic influences on working memory and executive functions have been reported (Kuntsi, et al., 2006; Stins, et al., 2005), with heritability estimates of 43-49% (Ando, Ono, & Wright, 2001). During an fMRI working memory study unaffected twins of schizophrenia patients showed activation and performance intermediate to their affected siblings and healthy controls (K. Karlsgodt, et al., 2007).

d) WM in schizophrenia

Meta-analyses of working memory performance in patients with schizophrenia revealed significant deficits across various WM-tasks (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005). The performance on various WM-tasks has been reported to correlate with negative and disorganised symptoms in schizophrenia patients (Cameron, et al., 2002). During WM for the identity of verbal items reduced activity in frontal and parietal regions was found to correlate with higher scores of negative and disorganized symptoms (Sanz, et al., 2009). Furthermore, reduced activity in frontal and subcortical regions was found to correlate with lower scores of positive symptoms and better social functioning (Sanz, et al., 2009). Working memory performance was found to be significantly worse in patients with schizophrenia compared with healthy controls (Brahmbhatt, Haut, Csernansky, & Barch, 2006). WM-performance of the patient's unaffected siblings was found to be neither different from controls nor the patients with schizophrenia (Brahmbhatt, et al., 2006). When these groups were matched on WM-performance task-related temporal cortex activity was reduced in patients with schizophrenia compared to unaffected siblings and healthy participants

(Brahmbhatt, et al., 2006). Changing the number of items to be maintained during the WM-task was less correlated with changes in brain activity in patients with schizophrenia than healthy controls (Johnson, et al., 2006). The degree of task-related activity of frontal-parietal (K. Karlsgodt, et al., 2007) and frontal-temporal (R. C. Wolf, Vasic, Hose, Spitzer, & Walter, 2007) regions in patients with schizophrenia has been shown to correlate with the degree of WM-performance deficit. These findings suggest that the adaptation of neural network activity in response to WM-capacity demands could be dysfunctional in patients with schizophrenia disrupting the relationship between WM-performance and WM-related brain activity. Reduced functional connectivity between bilateral superior parietal cortex and parietal-occipital cortices during WM for the location of non-verbal items was found to correlate with higher scores of positive symptoms (Henseler, Falkai, & Gruber, 2009). During WM for the identity of verbal items altered frontal-temporal connectivity has been found in people with prodromal symptoms of schizophrenia that were even more pronounced in first-episode patients with the disorder (Crossley, et al., 2009). Together these findings suggest some relation between WM-deficits and the symptomatology of schizophrenia. Because deficient working memory is also characteristic for people at risk for schizophrenia (Conklin, Curtis, Katsanis, & Iacono, 2000; Hambrecht, Lammertink, Klosterkotter, Matuschek, & Pukrop, 2002; Park, Holzman, & Goldman-Rakic, 1995) and persists even after amelioration of psychotic symptoms (Snyder, et al., 2008) it may be a suitable endophenotype closer linked to the underlying neuropathological mechanisms and genetic risk factors than psychotic symptoms.

e) Facial emotion processing in schizophrenia

For accuracy of facial memory and emotion processing, significant heritability estimates have been obtained (Gur, et al., 2007). Impaired processing of facial emotion with respect to the identification or differentiation of facial emotions has consistently been shown in patients

with schizophrenia (C. G. Kohler, Walker, Martin, Healey, & Moberg, 2009). Stronger impairment of facial emotion processing was shown to correlate with more negative and positive symptoms (C. G. Kohler, et al., 2009). Whether these deficits in facial emotion processing depend on the type of facial emotion (neutral, angry, happy, sad, fearful, disgusting and surprised) remains controversial with considerable variability across studies (Bediou, et al., 2005; Bigelow, et al., 2006; C. Kohler, et al., 2003; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Tsoi, et al., 2008). During the identification of facial emotions patients with schizophrenia performed worse than their healthy siblings and both performed worse compared to healthy controls (Bediou, Asri, et al., 2007). Further despite the improvement of clinical symptoms, performance deficits in facial emotion recognition persisted in patients (Bediou, Asri, et al., 2007). ERP-related activity over temporal areas was reduced in patients with schizophrenia compared to controls during the facial emotion but not during the gender identification task (Bediou, Henaff, et al., 2007). While over frontal areas ERP-signals were reduced in patients compared to controls for both tasks (Bediou, Henaff, et al., 2007). Moreover ERP-signal modulations by the type of facial emotion observed over frontal, temporal and occipital regions in healthy participants were absent in patients (Bediou, Henaff, et al., 2007).

Patients with schizophrenia compared with age-and gender- matched controls showed reductions of BOLD-response in amygdala, fusiform, inferior frontal, middle temporal and middle occipital gyrus during facial emotion processing (Johnston, Stojanov, Devir, & Schall, 2005). Because facial emotion processing is heritable, related to the symptomatology of schizophrenia and abnormal at both behavioural and neurophysiological levels in patients with schizophrenia and their relatives it may be an interesting endophenotype for schizophrenia.

f) Emotion and WM

It has been suggested that WM performance could be enhanced for stimuli with emotional compared to non-emotional content (Kensinger & Corkin, 2003). The immediate identification of schematic facial emotions was shown to be more accurate and rapid for happy and neutral compared to sad in healthy participants (Leppänen & Hietanen, 2004). Recently we have shown that WM performance for face identity (after one second delay) is modulated by the type of facial emotion in healthy volunteers (M. C. Jackson, Wu, Linden, & Raymond, 2009; M. Jackson, Wolf, Johnston, Raymond, & Linden, 2008). At the level of neural networks we found significant effects of emotional expressions on WM-related activity in prefrontal and temporal areas (M. Jackson, et al., 2008). However the facial emotion (happy, angry and neutral) for which WM performance was superior differed between individuals and samples studied (M. C. Jackson, et al., 2009; Langeslag, Morgan, Jackson, Linden, & Van Strien, 2009) indicative of considerable interindividual variability.

In summary patients with schizophrenia show significant impairments in visual working memory as well as facial emotion processing tasks that have been related to abnormal functioning of prefrontal and temporal regions. Furthermore, in healthy adults, working memory capacity for face identity benefits from emotional expressions through the engagement of temporal and prefrontal areas. However the type of emotional expression associated with superior working memory performance varies considerable between individuals. Genetic variability contributes to interindividual differences in face memory and emotion processing. Because the genetic risk for schizophrenia is continuous (Burns, 2008; H Verdoux & Cougnard, 2006), disorder-related gene variants that are common in the normal population could also contribute to interindividual variability in emotion-cognition interactions observed in unaffected individuals. Working memory for emotional faces thus appears to be an interesting endophenotype to investigate genetic contributions to variability

in emotion-cognition interactions in healthy individuals as well as in patients suffering from schizophrenia.

Genetic variables that affect proteins involved in neuroplasticity link schizophrenia and working memory

Genes and non-coding sequences involved in the regulation of neuroplasticity can influence adaptability in response to environmental stimuli across functional levels and are implicated in schizophrenia. Cognitive functions depend on the regulation of appropriate changes at the involved functional levels. Therefore genetic and epigenetic interindividual variability that affects the regulation of adaptability may contribute to interindividual differences at these levels. Patients with schizophrenia may suffer from a limited adaptability across functional levels due to dysfunctional adaptation mechanisms. Adaptation mechanisms could be dysfunctional because of primary changes in regulatory genes and non-coding sequences. Such dysfunctions could also be the result of secondary changes caused by the interactions of regulators with their targets and their regulation by environmental factors. The responsiveness of regulators to environmental factors could explain the impact of stress, drugs, infections, etc. in the manifestation of the genetic propensity to schizophrenia.

Neuropathological studies in schizophrenia have identified changes at molecular, cellular and neural network levels suggesting the dysfunction of regulatory mechanisms in neurodevelopment, neurotransmission and neuroplasticity (Harrison & Weinberger, 2005; D. Lewis & Lieberman, 2000; Owen, Williams, & O'Donovan, 2004b; Perlman, Weickert, Akil, & Kleinman, 2004; Ross, et al., 2006). Importantly these regulation mechanisms interact with environmental factors and thus could also explain the contribution of stress, drug abuse and infections to the susceptibility for schizophrenia. Findings at the individual neurofunctional levels are interlinked. For example anatomical and functional abnormalities in prefrontal and orbital-frontal cortex, parietal, temporal cortex and subcortical regions (Ross, et al., 2006)

could be related to reduced cell body size, myelination, numbers of dendritic spines and synaptic terminals of pyramidal neurons observed in hippocampus and neocortex (Harrison & Weinberger, 2005). Further deficient neuronal migration, survival and connectivity in neocortical areas during neurodevelopment (Harrison & Weinberger, 2005) and activity-dependent neuronal adaptations could be linked to the dysregulated expression of neuroplasticity-related genes. Variability in genes encoding proteins involved in neuroplasticity, neurotransmission and neurodevelopment (e.g. neuregulin-1 and dysbindin-1) has been linked to both working memory and schizophrenia. Neuroplasticity-related genes have been indicated in schizophrenia by genetic linkage and association studies as well as due to changes in the composition and function of synaptic proteins in those brain areas with functional and structural abnormalities (Ross, et al., 2006).

The dysregulation of synaptic plasticity involving particularly glutamatergic, dopaminergic and GABAergic transmission of prefrontal-temporal circuits has been implicated in schizophrenia (Lisman, et al., 2008). The interaction between glutamatergic and dopaminergic signalling is crucial for the generation and maintenance of neural activity in prefrontal and related networks that regulates neuronal adaptations critical for working memory and other cognitive functions (Castner & Williams, 2007). During working memory the involvement of dopaminergic transmission has been shown in PFC and hippocampus of humans (Aalto, Bruck, Laine, Nagren, & Rinne, 2005). The activity of dopamine receptors contributes to the glutamatergic regulation of GABAergic interneurons in PFC which may be important to regulate the activity of prefrontal circuits involved in working memory (Yuen & Yan, 2009).

NMDA receptor antagonists, such as ketamine or phencyclidine, reproduce some of the positive, negative, and cognitive symptoms of schizophrenia (Lisman, et al., 2008). Within the hippocampus formation hypofunction of NMDA receptors located on GABAergic interneurons may contribute to a reduction in GABA-mediated inhibition of pyramidal neurons (Lisman, et al., 2008). Such disinhibition in the hippocampus region could induce

hyperfunction of dopaminergic neurotransmission affecting various brain regions (Lisman, et al., 2008). Hyperactivation of the dopamine system has been related to psychosis and may interfere with the processing of sensory stimuli and working memory (Lisman, et al., 2008).

67-kDa glutamic acid decarboxylase (GAD67) encoded by *GAD1* is one of the GABA synthesizing protein isoforms in GABAergic neurons (Akbarian & Huang, 2006). SNPs residing in the non-protein coding sequences of *GAD1* have been linked to schizophrenia susceptibility, cortical gray matter reduction (Addington, et al., 2005), variability in GAD67 mRNA levels, and cognitive functions in patients (Straub, et al., 2007). It has been shown that NMDA receptor inhibition reduces GAD67 mRNA levels while the blockade of dopamine 1 and 2 receptors increases *GAD67* transcription including areas such as prefrontal and parietal cortex (Qin, Zhang, & Weiss, 1994). This indicates the regulation of GABA metabolism in cortical interneurons through antagonistic effects of glutamatergic and dopaminergic transmission. GAD67 transcription and translation are changed in prefrontal, temporal and visual cortex of patients with schizophrenia (Akbarian, et al., 1995; Dracheva, Elhakem, McGurk, Davis, & Haroutunian, 2004; Impagnatiello, et al., 1998; Volk, Austin, Pierri, Sampson, & Lewis, 2000). A correlation was also reported between reduced GAD67 and reduced BDNF (brain-derived neurotrophic factor)/ TrkB (tyrosine kinase B) receptor mRNA levels in PFC of patients with schizophrenia (T. Hashimoto, et al., 2005). Diminished activation of TrkB receptors could reduce the inhibition mediated by GABAergic interneurons in the PFC and thus compromise neural activity in its target regions. Both BDNF and TrkB transcription are regulated by neuronal activity (Nagappan & Lu, 2005; Zafra, Hengerer, Leibrock, Thoenen, & Lindholm, 1990). Increased BDNF transcription is mediated through the activation of glutamate receptors while reduced BDNF transcription dependents on activation of GABA receptors (Zafra, Castren, Thoenen, & Lindholm, 1991). Interestingly BDNF enhances presynaptic glutamate release only if the postsynaptic neuron is

glutamatergic or excitatory but not if the postsynaptic neuron is GABAergic or inhibitory (Schinder, Berninger, & Poo, 2000) which promotes its own transcription.

Patients with schizophrenia showed alterations in mRNA expression and composition of NMDA subunits in prefrontal, temporal, occipital (Akbarian, Sucher, et al., 1996; Beneyto, Kristiansen, Oni-Orisan, McCullumsmith, & Meador-Woodruff, 2007; Beneyto & Meador-Woodruff, 2008; Dracheva, et al., 2001; Gao, et al., 2000; Grimwood, Slater, Deakin, & Hutson, 1999; Kristiansen, Beneyto, Haroutunian, & Meador-Woodruff, 2006), and increased receptor density in superior temporal but not in prefrontal cortex (Nudmamud and Reynolds, 2001). Variability in the promoter region of *GRIN1*, which encodes the NMDA receptor subunit NR1 (Begni, et al., 2003; Georgi, et al., 2007) and *GRIN2B*, which encodes the NR2B subunit (D. Li & He, 2007), may influence schizophrenia susceptibility. However up to the present no evidence suggests a relationship between genetic variability in *GRIN1*/*GRIN2* and the observed differences in NMDA receptor subunit expression observed in patients. This supports the idea that other factors involved in the regulation of NMDA receptor expression may be altered in schizophrenia. Levels of postsynaptic density proteins known to interact with NMDA receptors were decreased while their mRNA levels were increased in prefrontal regions of patients with schizophrenia (Kristiansen, et al., 2006). The composition of NMDA receptor subunits is regulated during development (Law, et al., 2003). Developmental studies in animals suggest that reduction of NMDA receptor function during a critical period of development can produce e.g. deficits in working memory (Stefani and Moghaddam, 2005). The regulation of the components, number and localization of NMDA receptors in response to neuronal activity that mediates some forms of long-term potentiation/ depression (LTP/D) and contributes to the development and plasticity of neural networks could be dysfunctional in schizophrenia (Lau & Zukin, 2007).

Suppression of NMDA receptor activation induced by neuregulin-1 (NRG-1) is increased in patients with schizophrenia compared to controls (Hahn, et al., 2006). Deficient signalling of

NRG-1 protein isoforms via ErbB receptors (Buonanno & Fischbach, 2001) could be involved in the hypofunction of AMPA and NMDA receptors (B. Li, Woo, Mei, & Malinow, 2007), developmental dysregulation of cell differentiation, migration, myelination and proliferation of oligodendrocytes and neurons in schizophrenia (Akbarian, Kim, et al., 1996; Akbarian, et al., 1993; Arnold, Ruscheinsky, & Han, 1997; Jakob & Beckmann, 1986). Isoform-specific changes of NRG-1 mRNA and protein expression have been observed in prefrontal cortex and hippocampus of patients with schizophrenia (Bertram, et al., 2007; R. Hashimoto, et al., 2004; Meyer, et al., 1997; Parlapani, et al., 2008). NRG-1/ epidermal growth factor receptor B4 (ErbB4) signalling has been shown to trigger dopamine release and to depotentiate early-phase LTP via activation of dopamine 4 receptors in the hippocampus that decreases surface expression of glutamate-1 receptor-containing AMPA receptors (Kwon, et al., 2008). In addition neuregulin-1 regulates the subunit expression of the nicotinic acetylcholine (Y. Liu, Ford, Mann, & Fischbach, 2001), GABA(A) (Okada & Corfas, 2004; Rieff, et al., 1999) and NMDA receptors (Ozaki, Sasner, Yano, Lu, & Buonanno, 1997). Convergent evidence suggests that variability in the NRG-1 gene (non-coding sequence) may contribute to the genetic susceptibility for schizophrenia (Stefansson, et al., 2003; Stefansson, et al., 2002; Yang, et al., 2003) while the specific alleles, SNPs and haplotypes linked to schizophrenia varied considerably between studies (Corvin, et al., 2004; Munafo, Attwood, & Flint, 2008; Thiselton, et al., 2004). Two risk markers (SNP8NRG221132 and SNP8NRG243177/rs6994992) have been associated with the transcription of distinct *NRG-1* isoforms in the hippocampus of patients with schizophrenia and controls (Law, et al., 2006). In initially healthy subjects at high risk of schizophrenia the risk TT-genotype of rs6994992 compared to the C/T and C/C genotypes was associated with the development of psychotic symptoms (auditory hallucinations or persecutory ideas) (Lawrie, Hall, McIntosh, Cunningham-Owens, & Johnstone, 2008). Furthermore decreased activity of prefrontal and increased activity of temporal cortex during a sentence completion task (in the absence of

effects on task performance) and decreased scores in an intelligence test were found comparing risk and non-risk-genotype carriers (Lawrie, et al., 2008). An effect on spatial working memory capacity was also reported for the SNP rs6994992 genotype (Stefanis, et al., 2007). Although in the absence of effects at the behavioural level, effects of a further *NRG-1* risk genotype (SNP8NRG221533/rs35753505) were found on activity in limbic structures in patients with schizophrenia during a working memory task (Kircher, et al., 2009). NRG-1-induced activation of AKT protein has been found to be decreased in patients with schizophrenia (Keri, Seres, Kelemen, & Benedek, 2009a) and decreased level of NRG-1-induced AKT activation predicted higher levels of delusional ideas and anxiety in healthy participants (Keri, Seres, Kelemen, & Benedek, 2009b). Interestingly *AKT1* is also one of the genes implicated in schizophrenia (Thiselton, et al., 2008). Both neuregulin-1 and dysbindin-1 proteins have been shown to activate the PI3-kinase[4]-PKB/AKT[5] intracellular signalling pathway involved in the regulation of neuronal functions and survival (B. S. Li, et al., 2003; Numakawa, et al., 2004).

Dysbindin-1 is another protein involved in the regulation of neuroplasticity (Guo, et al., 2009; Talbot, et al., 2006) and *DTNBP1* (dysbindin/dystrobrevin-binding protein 1 gene) has been implicated as one of the top candidate genes for schizophrenia (Allen, et al., 2008). Dysbindin-1 directly interacts with 31 proteins involved in cell morphology, cellular development, intracellular and synaptic signalling located in synaptic vesicles, postsynaptic densities and microtubules (Guo, et al., 2009; Talbot, et al., 2006). The high relevance of *DTNBP1* for schizophrenia could be linked to the multiple interactions of dysbindin-1 with other proteins in neuronal inter-and intracellular signalling pathways. Genetic variability in *DTNBP1* has been linked to performance differences in spatial working memory and higher cognitive functions between patients with schizophrenia (Burdick, et al., 2006; Donohoe, et al., 2007).

[4] Phosphatidylinositol 3-kinase
[5] Protein kinase B (a serin-threonin kinase)

Reduced levels of dysbindin-1 mRNA or protein have been found in key regions of schizophrenia pathology such as the hippocampus (Talbot, et al., 2004; Weickert, Rothmond, Hyde, Kleinman, & Straub, 2008) and DLPFC (Weickert, et al., 2004) of patients with schizophrenia. Underexpression of dysbindin in glutamatergic presynapses of the hippocampus from patients with schizophrenia (Talbot, et al., 2004) could be one possible molecular mechanism contributing to impaired synaptic plasticity.

In the hippocampus of dysbindin-1 knockout mice, reduced dopamine levels and increased dopamine turnover have been observed (Murotani, et al., 2007). Loss of dysbindin-1 expression affected the size and density of synaptic vesicles, the size of synaptic cleft, the thickness of postsynaptic densities, and the amplitude of evoked excitatory postsynaptic currents (eEPSCs) of glutamatergic pyramidal neurons in the hippocampus (X. W. Chen, et al., 2008). Further knockdown of dysbindin expression has been shown to affect the organization of actin filaments of the cytoskeleton and phosphorylation of c-Jun N-terminal kinase which regulates neurite outgrowth (Kubota, et al., 2008).

In addition impaired neurite outgrowth has been demonstrated in cultured hippocampal neurons from mice deficient of BLOC-1 a dysbindin-1 containing multi-protein complex (Ghiani, et al., 2009). BLOC-1's interaction with SNARE complexes (Ghiani, et al., 2009) supports its role in axonal growth (Chua & Tang, 2008; Hirling, et al., 2000; Osen-Sand, et al., 1993) and synaptic vesicle exocytosis (Jahn & Scheller, 2006). Dysbindin protein levels have been shown to regulate the expression of SNAP-25 (synaptic membrane synaptosome-associated protein of 25kDa, member of the SNARE complex) and Synapsin-I a synaptic vesicle-associated cytoskeletal protein) (Numakawa, et al., 2004). BLOC-1 and AP-3 (adaptor protein 3) complexes regulate protein trafficking to lysosome-related organelles (Setty, et al., 2007), e.g. targeting proteins to the membrane surface (Dell'Angelica, Shotelersuk, Aguilar, Gahl, & Bonifacino, 1999; Salazar, et al., 2006).

Furthermore reduction of this protein has been associated with enhanced phasic, reduced tonic dopaminergic, reduced glutamatergic and GABAergic neurotransmission in PFC and decreased WM-performance in mice (Jentsch, et al., 2009; Ji, et al., 2009; Murotani, et al., 2007; Takao, et al., 2008). Consistent with dysbindin's function in the BLOC-1 complex involved in protein trafficking to lysosomes the inhibition of dysbindin protein expression has been shown to up-regulate the surface expression of dopamine 2 receptor (D2R) in cortical neurons presumably by blocking D2R traffic to lysosomes for its degradation (Ji, et al., 2009). More recently similar effects of dysbindin protein levels have been shown on the surface expression of NMDA receptor subunit NR2A presumably through the regulation of lysosome-dependent degradation, on the amplitude and decay time of evoked NR2A-dependent excitatory postsynaptic potentials and the magnitude of LTP in hippocampal pyramidal neurons (Tang, et al., 2009).

Variability in non-coding sequence of *DTNBP1* has been linked to mRNA changes in regions such as PFC, hippocampus and amygdala of the normal human brain (Weickert, et al., 2004) as well as to normal individual variability in cognitive performance and brain function (Burdick, et al., 2006; Fallgatter, et al., 2006).

Another pre-and postsynaptically expressed protein (Paspalas, Selemon, & Arnsten, 2009) implicated in schizophrenia pathogenesis and working memory functions, and operating through the regulation of intracellular and synaptic signalling is regulator of G-protein signalling 4 (RGS4). RGS4-accelarated GTP-ase activity regulates the effects of metabotropic G-protein-coupled receptor activity on various intracellular signalling pathways, e.g. mitogen-activated/extracellular-regulated protein kinase (MAPK/ERK) and AKT signalling (Traynor & Neubig, 2005).

RGS4 gene expression at varying levels has been detected within inferior, superior frontal and cingulate cortex, insular and inferior temporal cortex, caudate, putamen and nucleus

accumbens, parahippocampal gyrus, CA-pyramidal region and thalamus of humans (Erdely, et al., 2004). Both RGS4 mRNA and protein levels are regulated through a variety of factors. Negative effects of phosphatidyl inositol triphosphate (PIP3) and phosphatidic acid on RGS4-mediated GTP-ase activity can be prevented by Ca^{2+}/Calmodulin (Traynor & Neubig, 2005). RGS4 mRNA levels are influenced by glucocorticoids, chronic stress in a brain region-specific manner (Ni, et al., 1999). Activation of D1 and D2 receptors exerts antagonistic effects on striatal RGS4 mRNA level (Taymans, et al., 2004). Down-regulation of RGS4 mRNA in striatum and medial PFC and protein in striatum by amphetamines has been observed (Schwendt, Gold, & McGinty, 2006). Furthermore this study found that amphetamine potentiated the D1 receptor antagonist-induced increase and the D2 receptor antagonist-induced decrease of RGS4 mRNA in the caudate putamen (Schwendt, et al., 2006). Effects of variability in the *COMT* gene on prefrontal and hippocampal RGS4 mRNA levels have also been reported in patients with schizophrenia and healthy controls (Lipska, et al., 2006).

In addition an interaction of *COMT* (Val158Met) and RGS4 (rs951436) genotype effects has been reported on DLPFC activity during working memory in healthy participants (Buckholtz, Sust, et al., 2007). Together these findings suggest the regulation of RGS4 mRNA levels through the convergent effects of environmental and genetic factors.

Reduction of RGS4 mRNA expression has been observed in prefrontal, visual and motor cortex of patients with schizophrenia, which also showed correlations of mRNA levels between regions (Mirnics, Middleton, Stanwood, Lewis, & Levitt, 2001). Recently a study investigated splice form-specific levels of RGS4 mRNA and found exclusively a reduction of the RGS4-3 isoform in DLPFC of patients with schizophrenia compared to controls (Ding & Hegde, 2009). Furthermore decreased expression of RGS4 protein in frontal cortex and mRNA in insular cortex, superior frontal, cingulate (Erdely, Tamminga, Roberts, & Vogel,

2006) and superior temporal gyrus (Bowden, Scott, & Tooney, 2007) was found in patients with schizophrenia compared to controls.

However, despite the consistently observed decrease of RGS4 mRNA and protein expression as well as association between common variants in non-coding sequence of the RGS4 gene and schizophrenia susceptibility (Talkowski, Chowdari, Lewis, & Nimgaonkar, 2006), none of these variants were associated with RGS4 mRNA levels in PFC and hippocampus in patients or in healthy controls (Lipska, et al., 2006). SNP rs10917670 and rs951439 have been associated with measures of face memory in a large sample of patients with schizophrenia and their relatives (Prasad, et al., 2009). SNP rs951439 has also been associated with frontoparietal and frontotemporal BOLD-response and functional connectivity during working memory as well as region-dependent alternations of gray and white matter volume (Buckholtz, Meyer-Lindenberg, et al., 2007).

In summary variation, in genes and non-coding sequences of several proteins involved in the regulation of neuroplasticity, specifically within glutamatergic, dopaminergic and GABAergic systems, has been associated with quantitative or qualitative changes at the transcription or translation level in schizophrenia. These changes may contribute to the functional and structural abnormalities at the neuronal and neural network level that underlie the impairment of cognitive processes observed in patients with schizophrenia. Because the genetic risk for schizophrenia is thought to be continuous, genetic variants that are common (minor allele frequency > 0.10) among healthy people and associated with the neuropathology of cognitive and/or affective deficits in schizophrenia could also contribute to the normal interindividual variability in emotion-cognition interactions. However it remains a huge challenge to identify those genetic variants exhibiting effects at neural and behavioural levels. Inconsistent and contradictory findings have been reported for virtually all genes, variants and alleles that have been associated with schizophrenia. This heterogeneity remains even if accounting for confounding factors such as age, gender or age-at-onset of the disorder and rather appears to

be characteristic for the genetics of complex human diseases. Moreover if the effects of genetic variants on neuronal gene and protein expression or function are unknown the interpretation of results will be hampered. Recently it was found that experience-driven neuronal activity-dependent changes in gene and protein expression regulate neuroplasticity involved in learning and memory (described in chapter 3) (Flavell & Greenberg, 2008; Greer & Greenberg, 2008). This suggests that the effects of genetic variability not only depend on the interactions with other genes, proteins, epigenetic and environmental factors but are also influenced by neuronal activity driven by sensory, cognitive, emotional or motor experiences, e.g. during interactions between the individual and its social environment. In order to account for the inconsistency and heterogeneity observed in genetic studies of schizophrenia we may therefore also require knowledge about how experience-driven neuronal activity contributes to changes in gene and protein expression to regulate neuroplasticity.

What is the rationale for using genetic neuroimaging for the investigation of endophenotypes?

How interindividual genetic variability contributes to interindividual differences at the level of neural networks and the related behavioural response, and how this can be altered in psychiatric disorders, are questions that can be addressed with genetic neuroimaging.

Genetic neuroimaging can provide more specific and reliable endophenotypes that may help identify the contribution of genetic predictors to a neurophysiological response and its cognitive or behavioural effects.

The assay of endophenotypic variations by fMRI has been used to supplement phenotype-genotype association, e.g. to investigate the effects of candidate genes for schizophrenia (J. Callicott, et al., 2005; Egan, et al., 2004; Straub, et al., 2007). This non-invasive, but physiological approach may help to quantify and specify the influence of genetic parameters on brain functions and behaviour. The neural network level accessed with fMRI is supposed

to be more directly associated with physiological parameters under the influence of genetic parameters than a complex psychiatric disorder for example. At the level of neural networks genetic effects have been detected even in the absence of behavioural differences in cognitive tasks (Blasi, et al., 2005; Canli, et al., 2005; Schott, et al., 2006). This suggests fMRI as one non-invasive method that can be applied to test for association between individual neurophysiological variation(s) and genotype variation(s) contributing to the understanding how genetic variation can impact functions at the neural network level (Hariri, Drabant, & Weinberger, 2006). Due to the correlative nature of this approach pre-validation of the genetic variables for effects on neurobiological functions and heritability of the endophenotype to some degree are paramount. This view has been propagated by the founders of genetic neuroimaging and researchers currently working with this approach (Hariri & Weinberger, 2003; A. Meyer-Lindenberg & D. R. Weinberger, 2006; Straub, et al., 2007). However with the improvement of imaging data analysis tools, reliability of genetic imaging may increase and thus could be used to identify new genetic variants (Potkin, et al., 2009).

Common genetic variants, which affect the expression or function of neuronal activity-regulated proteins and ncRNAs involved in neuroplasticity, are rarely known. Individual variation of endophenotypes likely depends on the complex interaction of genetic, epigenetic and environmental factors whereas for the most part each individual factor confers only a moderate effect. The neurobiological function for the majority of transcription and translation products is still unknown.

So far the genetic contribution to individual variation of neuronal network activity involved in cognitive functions has been investigated for genes encoding receptors or enzymes of several neurotransmitter systems as well as BDNF (Egan, et al., 2003; T. Goldberg & Weinberger, 2004). The majority of those studies focused on two common polymorphisms 5-HTTLPR (*SLC6A*) within non-coding and COMT-Val^{158}Met within protein-coding sequence of the serotonin transporter respectively the catechol-O-methyltransferase gene. Both

polymorphisms affect the protein expression level and in case of COMT-Val^{158}Met additionally the enzyme activity. Effects of genetic variability on brain activity were found in the absence of task-related behavioural effects and in a priori selected regions of interest (ROIs). Consistently, the 5-HTTLPR genotype has been reported to account for variability of amygdala activity in response to various tasks contrasting emotional stimuli (A Bertolino, et al., 2005; Canli, et al., 2005; Hariri, et al., 2005; Hariri, et al., 2002; Heinz, et al., 2005; Heinz, et al., 2007; Smolka, et al., 2007). However observed differences for emotion contrasts have been shown to be driven by a general increase of brain activity in individuals with the low-5-HTT expression genotype (Canli, et al., 2005). Recently, this genotype has been linked to performance in executive function tasks with conflicting results (Borg, et al., 2009; Paaver, et al., 2007). Using similar, attention or memory tasks an effect of the COMT-Val^{158}Met genotype has been found on activity in various brain regions (Blasi, et al., 2005; Drabant, et al., 2006; Egan, et al., 2001; Ho, Wassink, O'Leary, Sheffield, & Andreasen, 2005; Schott, et al., 2006; Smolka, et al., 2005). The majority of behavioural studies found better cognitive performance in various tests associated with the low-COMT activity Met-allele (Savitz, Solms, & Ramesar, 2006) while this allele has been also associated with less efficient emotional processing in prefrontal and limbic regions (Drabant, et al., 2006; Smolka, et al., 2005). Such balance between advantageous and disadvantageous effects of the COMT-Val^{158}Met polymorphism may explain the almost 50/50 ratio of population allele frequencies. Combined additive effects of both polymorphisms including a second 5-HTT polymorphism (rs25531) that also affects 5-HTT mRNA expression, have been observed on activity in limbic regions during processing of emotional pictures (Smolka, et al., 2007). Also non-additive effects of polymorphisms within the COMT gene including Val^{158}Met (A Meyer-Lindenberg, et al., 2006) as well as Val^{158}Met in COMT and the rs6465084 polymorphism in the glutamate receptor 3 gene have been shown to modulate the working memory-related response of prefrontal networks (H. Tan, et al., 2007). COMT contributes to the availability of

catechols and some other hydroxylated metabolites e.g. catecholamines and catecholestrogens (Männistö & Kaakkola, 1999) and 5-HTT influences synaptic levels of 5-HT (Heinz, et al., 2000; K. Lesch, et al., 1996; Murphy, Lerner, Rudnick, & Lesch, 2004) and other monoamines. By influencing the levels of these neurotransmitters and thus neural network activation, COMT has been suggested to modulate cognitive performance (A. Meyer-Lindenberg & D. Weinberger, 2006) or emotion processing (Smolka, et al., 2005) and 5-HTT emotional regulation (Canli & Lesch, 2007; Hariri & Holmes, 2006). It remains unclear how COMT and 5-HTT interact with other regulators of these transmitters and how regulators of COMT and 5-HTT contribute to their expression level and activity.

The statement "COMT is a major enzyme in prefrontal areas because of a lack of the dopamine transporter in this region" (Krämer, et al., 2007) reflects a common misconception about the role of this enzyme in catecholamine metabolism. Most available evidence suggests that both isoforms of COMT are intracellular. More specifically, the membrane-bound MB-COMT has been localised to the rough endoplasmatic reticulum, and the soluble S-COMT to the cytosol and nucleus (Ulmanen, et al., 1997). If COMT is inside the cell the enzyme's access to synaptic dopamine depends on the availability of a reuptake mechanism. The lack of dopamine transporters in prefrontal cortex would thus severely limit the function of COMT if it were not for at least two reasons. First, norepinephrine transporters also transport dopamine (Horn, 1973), having a higher affinity for dopamine than does the dopamine transporter (Eshleman, et al., 1999; H. Gu, Wall, & Rudnick, 1994). Second, dopamine reuptake in prefrontal cortex depends primarily on the norepinephrine transporter (Morón, Brockington, Wise, Rocha, & Hope, 2002).

COMT does seem to play an important role in prefrontal cortex, judging from the expression of its mRNA, which is higher than in the striatum (Matsumoto, Weickert, Beltaifa, et al., 2003), and this seems to be inversely related to the expression of dopamine transporters

(Moll, et al., 2000). It is thus tempting to reformulate the above sentence into "COMT is a major enzyme in prefrontal areas *despite* a lack of the dopamine transporter in this region".

Variations and reduced mRNA expression in *COMT* (A. Bertolino, et al., 2004; N. J. Bray, et al., 2003; Egan, et al., 2001; Matsumoto, Weickert, Akil, et al., 2003; Shifman, et al., 2002; Talkowski, et al., 2008; H. J. Williams, Owen, & O'Donovan, 2007) and less convincingly in *5-HTT* (Dubertret, Hanoun, Ades, Hamon, & Gorwood, 2005; Golimbet, et al., 2004; Hranilovic, et al., 2004; Zaboli, et al., 2008) have been implicated as contributors to the susceptibility for schizophrenia or deficits in schizophrenia. Further dopaminergic (Sesack & Carr, 2002) and serotonergic dysfunction (Geyer & Vollenweider, 2008) as well as their interaction (Esposito, Di Matteo, & Di Giovanni, 2008) have been linked to schizophrenia and to cognitive and affective symptoms in schizophrenia.

The transcription, expression and activity of 5-HTT in neurons are regulated by multiple factors, including hormones, protein kinases, receptor activation (Blakely, De Felice, & Hartzell, 1994), the SNARE protein syntaxin 1A (Quick, 2003) and concentration of 5-HTT substrates. COMT mRNA expression is upregulated by hypoxia (X. C. Lu, et al., 2004) and COMT activity is inhibited by glucocorticoids in the hypophysis and hypothalamus (Parvez & Parvez, 1973). Although limited the knowledge about the regulation of COMT and 5-HTT suggests that the action of COMT and 5-HTT is influenced by regulators while their own influence is restricted to the regulation of their substrates. Conflicting findings regarding the effects of genetic variability in *COMT* and *5-HTT* may be due to the effects of regulators.

Nevertheless studies combining genetics and fMRI have consistently demonstrated that variability in the genes encoding COMT and 5-HTT influences the activation of brain regions involved in cognitive and emotional processing in humans. However the outcome of these genetic differences appears to depend on additional regulatory factors and variability in other genes not yet sufficiently understood. Investigating these factors may also clarify the relation between genetic variability in COMT/5-HTT genes and schizophrenia vulnerability.

Only a few studies have used the combination of genetics and fMRI to investigate effects of genetic variability on endophenotypes such as working memory at the neural network level in patients with schizophrenia (Diaz-Asper, et al., 2008; Kircher, et al., 2009; Meda, et al., 2009; Potkin, et al., 2009; Roffman, et al., 2008). However using this approach appears suitable for the investigation of genetic influences on working memory for emotional faces in healthy participants and patients with schizophrenia

Notes on general methodical issues

a) Selection of genes and their genetic variants related to the selected endophenotype

For the choice of endophenotype relevant genetic variants, we considered genetic (variability, frequency, mRNA and protein expression) and neuro-physiological (effects on function and structure of brain regions and neurons) aspects of proteins involved in neuroplasticity (with focus on the neurotransmitters glutamate, dopamine, GABA, serotonin), associated with cognitive functions (particularly related to WM, emotion and face processing) and susceptibility to schizophrenia.

Literature was searched to identify genetic variants based on convergent evidence for their likely involvement in modifications of neuroplasticity (intracellular signalling, synaptic transmission, neuronal structures) and their relevance to variability/deficits in cognitive functions and/or pathogenesis/risk of schizophrenia.

From the literature, the following information regarding cognitive functions or schizophrenia and other related disorders was used to select a number of genetic variants: function of the protein, related transmitter system(s), gene(s), chromosomal location of the gene, polymorphism(s)/ haplotypes, with respect to frequency (common minor allele frequency > .10/ large difference between cases and controls), ethnicity (preferentially SNP data available

for Caucasian and UK samples), type of polymorphism, effects on mRNA and protein level, assumed functional effects, link with schizophrenia/cognition/emotion and animal model(s). As a result a primary list of genetic variants was generated (please refer to **appendix A**).

b) Acquisition of methodical information to identify the selected genetic variants

Another criterion for the selection of genetic variants was the availability and feasibility of methods to identify the genetic information of interest. For this purpose literature and gene banks were searched to provide information about the identity number of genes, the identity number of specific genetic variants (rs number), the sequences of primers and other important procedure details (**appendix B**).

After combining the information generated in the first list and procedure details, 8 first and 9 second choice genetic variants in 15 different genes concerning four transmitter systems were proposed as potential candidates of investigation. The distinction into first and second choice was made for the case in which some of the first choice variants were not feasible due to technical reasons. Then variants from the second choice list were used to ensure the final number of variants would not be smaller than 9 rather larger. This first proposal was revised and modified together with our collaborator C. Kissling according to practicability of the molecular genetic techniques (genotyping only based on restriction enzymes; preferably already established) and led to a final selection of 9 genetic variants in 8 different genes (**appendix C**). The rational for the final selection of these 8 genes has been given above (please refer to "Genetic variables that affect proteins involved in neuroplasticity link schizophrenia and working memory" and "What is the rationale for using genetic neuroimaging for the investigation of endophenotypes?".

c) Definition of three participants groups

The definition of participant cohorts according to their ethnicity is necessary to avoid faulty associations and increase the chance to detect a true association. The reason is the presumably small size of genetic effects. Variability arising from typically large effects, like age, gender, IQ, etc. should be minimised because they can easily obscure these small potential gene effects. The combination of a genetic and imaging association study in cases (patients) and controls is susceptible to population stratification artefacts and ethnic matching within groups is potentially critical (Hariri & Weinberger, 2003). Thus, ethnicity and other confounding factors should be carefully controlled across compared groups/ individuals. We included age, gender, education, handedness and ethnicity as possible confounding factors.

Participants of the combined fMRI-Genetic study were divided into three groups of Caucasian adult subjects. One group of Caucasian patients with schizophrenia, two groups of healthy controls comprise one Caucasian European and one Caucasian Welsh sample.

For all patients basic clinical parameters (age at onset, years of illness, diagnosis and current medication) were documented. All patients were interviewed with the MINI International Neuropsychiatric Interview and the Positive and Negative Symptom Scale for current psychopathology (PANSS) involving questions about current and past symptoms in collaboration with Stefanie Linden (M.D.; psychiatrist). Patients were also tested with the National Adult Reading Test, Schizotypal Personality Questionnaire and the PC-based version of the emotional working memory task (to estimate performance) before their participation in the combined fMRI-Genetic study.

Control participants were interviewed (C.W.) prior to the experiment to exclude any neurological or psychiatric disease of participants or their relatives as well as MRI contra-indications (**appendix E**).

Participants in the Welsh sample needed to fulfil the following criterion: all their four grandparents were born in Wales. This group was created to allow for closer ethic matching with the patient group.

In order to allow matching for age and education, the control sample was designated to cover a broad age range from 18 to 50 years. Initially, 25 subjects for each control group and 15 schizophrenics for the patient group were strived for the study. Because we were unable to recruit more than 8 patients who agreed to be scanned and also performed the task above chance level the investigation of genetic influences on brain function and behaviour in schizophrenia couldn't be realized. Instead we focused on our large control sample (combining the Welsh and European Caucasian samples) to investigate genetic influences on interindividual differences in emotional working memory.

d) The course of data analysis

First behavioural and fMRI data was analysed to test the effects of emotion and load on WM performance (d'prime values averaged across load for each emotion/ averaged across emotion for each load/ overall performance across all 12 conditions/ d'prime mean difference between emotions), WM capacity (Cowan's K and Cowan's Kmax for each emotion) and its neural correlates (beta values averaged across load for each emotion/ across emotion for each load/ beta differences between emotions). Both performance and imaging measures were tested for correlations to reveal task-performance/brain activity relationships comparing the different emotions.

BQX imaging data analysis software did not allow the inclusion of one between- subject factor and two within-subject factors and even later when such design became feasible the large amount of volume time course files (218) probably led the program to crash. Besides, the calculation of this data-intense GLM-analysis was impossible with a standard Windows-driven system due to insufficient working memory for the calculation.

Hence we choose a step-wise approach, based on the first-level RFX-GLM we computed a second-level RFX-within-subject two-factors ANOVA, extracted the beta values from all significantly activated clusters (ROIs). Further analysis of these values combined with behavioural and genetic data was executed in SPSS.

We were particularly interested in happy and angry faces because in previous studies the majority of participants showed WM performance benefits for happy and angry compared to neutral faces (M. C. Jackson, et al., 2009; M. Jackson, et al., 2008; Langeslag, et al., 2009). However, we had noted considerable interindividual variability, motivating the current study of its genetic basis. Genotype effects on WM performance differences were all $p > .13$ except for DTNBP1 for the mean d'prime difference between happy and neutral and for SLC6A4 for the mean d'prime difference between angry and happy $p < .05$ (**Tab.1**). However, none of the regions that showed significant activity for the angry-happy contrast showed significant correlations between brain activity (beta difference) and performance (d'prime difference) for the difference between angry and happy (all p's $> .19$; **Appendix D**). For this reason SLC6A4 genotype effects on the WM performance difference between angry and happy were not followed up at the neural network level because our primary aim was to explain the interindividual differences for the emotion effect on WM. However we did find significant correlations between brain activity (beta difference) and performance (d'prime difference) for the difference between happy and neutral in the FFA, ITG and STS of the right hemisphere (all p's $< .05$; **Tab.2** Experimental chapter I) and additionally a number of regions that showed significant correlations between brain activity (beta difference) and performance (d'prime difference) for the difference between angry and neutral or/and significant correlations between brain activity (beta mean) and performance (d'prime mean) for happy and/or angry faces (**Tab.2** Experimental chapter I). Only these regions with significant activity-performance correlations were analysed for effects of DTNBP1 genotype on brain activity. This allowed us to test whether the observed DTNBP1 genotype effects on the

interindividual variability of emotion effects on WM performance could be explained by genotype-dependent differences of performance associated brain activity. In this way we further reduced the number of genetic variants from our selection of 9 genetic variants in 8 different genes that was based on their neurobiological plausibility for involvement in WM and emotional processing by identifying which variants could explain the interindividual variability of emotion effects on WM performance and associated brain activity. Furthermore our results of dysbindin-1 genotype effects on emotion-dependent WM performance and related brain activity are in agreement with reports in the literature regarding dysbindin-1 mRNA distribution in human brain, effects of this genotype on dysbindin-1 mRNA levels in normal brain, changes in dysbindin-1 mRNA and protein levels in brain tissue of patients with schizophrenia. For these reasons we decided to focus on dysbindin-1 and not to pursue any further the analysis of the other genetic variants. Genotype and allele frequencies for all 9 genetic variants can be found in Appendix D. Allele frequencies for all SNPs have been checked with Chi^2-test (5%; DF = 2) and population is in HWE.

Table 1. Genotype effects on WM performance (d'prime mean differences for angry minus neutral, happy minus neutral and angry minus happy).

Genotype	angry-neutral	happy-neutral	angry-happy
DTNBP1	$F(54,1) = 0.31$ $p = .58$	$F(54,1) = 4.31$ $p = .04$	$F(54,1) = 2.23$ $p = .14$
SLC6A4	$F(53,2) = 2.03$ $p = .14$	$F(53,2) = 0.20$ $p = .82$	$F(53,2) = 3.57$ $p = .04$
RGS4	$F(53,2) = 0.06$ $p = .95$	$F(53,2) = 0.37$ $p = .69$	$F(53,2) = 0.13$ $p = .88$
NRG1	$F(53,2) = 0.42$ $p = .66$	$F(53,2) = 0.06$ $p = .94$	$F(53,2) = 1.09$ $p = .35$
GRIN1	$F(54,1) = 0.27$ $p = .61$	$F(54,1) = 0.11$ $p = .74$	$F(54,1) = 0.07$ $p = .80$
GRIN2B	$F(53,2) = 0.33$ $p = .72$	$F(53,2) = 0.16$ $p = .86$	$F(53,2) = 0.09$ $p = .92$
COMT(Val/Met)	$F(53,2) = 0.74$ $p = .48$	$F(53,2) = 0.10$ $p = .91$	$F(53,2) = 0.71$ $p = .45$
COMT rs4818	$F(53,2) = 0.33$ $p = .72$	$F(53,2) = 1.10$ $p = .34$	$F(53,2) = 0.30$ $p = .74$
GAD1	$F(53,2) = 0.04$ $p = .96$	$F(53,2) = 0.14$ $p = .87$	$F(53,2) = 0.41$ $p = .67$

Contributors

The imaging paradigm was designed by M.C. Jackson and D.E.J. Linden; fMRI experiments of the control sample were performed and analyzed by M.C.J. and C. Wolf; ethics approval for the genetic imaging study for both patient and controls was obtained by D.E.J.L. and C.W.; blood samples were taken by Tony Bedson (radiographer), D.E.J.L. or S.C. Linden; blood sample tracking, storage and transport was organized by C.W.; fMRI experiments of the patient sample were performed, analyzed by C.W. and interpreted by D.E.J.L. and C.W.; the genetic variants were selected by C. Kissling and C.W.; A. Baird., C.K. and C.W. contributed to genetic data analysis; the combined analysis of imaging and genetic, behavioural and genetic data was executed by C.W. and interpreted by D.E.J.L., M.C.J. and C.W.; control participants were recruited by M.C.J. and C.W.; patients were recruited and assessed by S.C.L. and D. Healy.; C.W. wrote all three manuscripts; D.E.J.L. and J. Thome supervised and provided the environment to realize the project and all authors contributed to and gave approval to the manuscripts.

The part in the general introduction about COMT has been published as an electronic letter in The Journal of Neuroscience under the title "The COMT conundrum" by C.W. and D.L. January, 2008. References for the individual articles/chapters are mutually listed at the end of the thesis.

Experimental Chapter I

Bridging the gap between synaptic function and cognition: A genetic imaging study of dysbindin-1 genotype effects on emotional working memory and cortical activity.

This chapter has been published in Molecular Psychiatry (C. Wolf, Jackson, Kissling, Thome, & Linden, 2009) with the following title and contributing authors and has been presented as a poster at the conference *Exciting Biologies 2008: Biology of Cognition* organized by Massachusetts General Hospital, Fondation Ipsen and Cell Press, at Château Hôtel Mont Royal, in Chantilly, France, October 16-18, 2008.

Dysbindin-1 genotype effects on emotional working memory.

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Running title: Dysbindin, emotional working memory, fMRI, schizophrenia

Keywords: dysbindin; genetic imaging; working memory; emotional faces; schizophrenia

Abstract

We combined functional imaging and genetics to investigate the behavioural and neural effects of a dysbindin-1 (*DTNBP1*) genotype associated with the expression level of this important synaptic protein, which has been implicated in schizophrenia. On a working memory (WM) task for emotional faces, participants with the genotype related to increased expression showed higher WM capacity for happy faces compared to the genotype related to lower expression. Activity in several task-related brain areas with known DTNBP1 expression was increased, including hippocampus, temporal and frontal cortex. Although these increases occurred across emotions, they were mostly observed in areas whose activity correlated with performance for happy faces. This suggests effects of variability in *DTNBP1* on WM capacity and region-specific task-related brain activation in humans. Synaptic effects of DTNBP1 implicate that altered dopaminergic and/or glutamatergic neurotransmission may be related to the increased WM capacity. The combination of imaging and genetics thus allows us to bridge the gap between the cellular/molecular and systems/behavioural level and extend the cognitive neuroscience approach to a comprehensive biology of cognition.

Introduction

Inter-individual variability of cognitive skills is explained to a considerable degree by genetic factors (Ando, et al., 2001; Blokland, et al., 2008). The combination of molecular genetics and functional imaging allows for the effects of genetic variation in neurobiologically relevant proteins on neurophysiological responses in cognition- and emotion-related neural networks to be investigated in humans (Hariri, et al., 2006).

Recent evidence suggests that variability in the dysbindin-1(dystrobrevin-binding protein 1) gene (*DTNBP1*; OMIM 607145) contributes to interindividual variability of cognitive functions at both neurophysiological and behavioural levels in healthy individuals as well as in patients with schizophrenia (Burdick, et al., 2006; Donohoe, et al., 2007; Donohoe, et al., 2008; Fallgatter, et al., 2006). For example, 12% of variance in spatial WM performance in patients with schizophrenia were accounted by the C-A-T dysbindin-1 haplotype (Donohoe, et al., 2007). At the molecular level, genetic variability markers in the *DTNBP1* gene, including SNP rs1047631 located in a 3'UTR (untranslated region) have been shown to index dysbindin-1 mRNA expression (Bray, Buckland, Owen, & O'Donovan, 2003; Bray, et al., 2005; Weickert, et al., 2004). The G-allele of SNP rs1047631 is associated with 17-19% increase of dysbindin-1 m-RNA levels (Bray, et al., 2005; Weickert, et al., 2004). Variability in non-protein coding sequences including UTRs has been proposed as a major source for interindividual differences of quantitative traits (J. Mattick & Makunin, 2006). Furthermore it has recently been reported that SNP rs1047631 is positioned within a microRNA binding site (Luciano, et al., 2009), which adds to the evidence that variability in this region is involved in gene regulation. Dysbindin-1 gene transcription has been observed in temporal neocortex, entorhinal cortex, orbitofrontal cortex, dorsolateral prefrontal cortex (DLPFC), amygdala and hippocampus of healthy adults, with higher abundance in gray than white matter (Weickert, et al., 2004). Reductions of dysbindin-1 mRNA in DLPFC (Weickert, et al., 2004), hippocampus (Talbot, et al., 2004; Weickert, et al., 2008) and

dysbindin-1 protein in glutamatergic pre-synapses of the hippocampus (Talbot, et al., 2004) have been reported in patients with schizophrenia. Glutamatergic synapses in these regions contribute to neuronal activity related to WM (Dégenètais, Thierry, Glowinski, & Gioanni, 2003; Wall & Messier, 2001). Therefore interindividual differences in dysbindin-1 protein levels at prefrontal and hippocampal synapses may contribute to interindividual variability in WM-related activity. Dysbindin-1 is involved in the regulation of neuroplasticity (Guo, et al., 2009; Talbot, et al., 2006) and has also been implicated as a candidate gene for schizophrenia (Allen, et al., 2008). Dysbindin-1 directly interacts with 31 proteins involved in cell morphology, cellular development, intracellular and synaptic signalling at its different locations in synaptic vesicles, postsynaptic densities and microtubules (Guo, et al., 2009; Talbot, et al., 2006). Recently BLOC-1 (Biogenesis of lysosme-related organelles complex-1) a dysbindin-containing multi-protein complex has been identified in the murine cerebral cortex, hippocampus and cerebellum (Ghiani, et al., 2009). Furthermore this study revealed the developmental regulation of cortical dysbindin protein expression and neurite outgrowth defects in hippocampal neurons of BLOC-1-deficient mice (Ghiani, et al., 2009). The relevance of *DTNBP1* for schizophrenia might be linked to the multiple interactions of dysbindin-1 with other proteins in neuronal inter-and intracellular signalling pathways, e.g. the PI3-kinase-PKB/Akt intracellular signalling pathway (Numakawa, et al., 2004). Interestingly, the *Akt1* gene has been implicated in schizophrenia as well (H. Y. Tan, et al., 2008; Thiselton, et al., 2008). Lack of dysbindin synthesis in Sandy mouse, a dysbindin-1 knockout (W. Li, et al., 2003), has been found to affect the vesicle structure and kinetics of synaptic glutamatergic transmission of pyramidal neurons in the CA1 region of the hippocampus (X. W. Chen, et al., 2008), to reduce evoked responses in prefrontal pyramidal neurons and to impair working memory performance (Jentsch, et al., 2009). Furthermore, knockdown of dysbindin expression has been shown to affect the organization of actin filaments of the cytoskeleton and phosphorylation of c-Jun N-terminal kinase, which regulates

neurite outgrowth (Kubota, et al., 2008). Increased dopamine turnover and reduced dopamine levels (Murotani, et al., 2007) in cortex and hippocampus have also been observed in Sandy mouse. In sum, there is converging evidence establishing a central role for dysbindin in the regulation of synaptic structure and function.

With its multiple effects on both neocortical and limbic areas, dysbindin is an ideal candidate protein for the regulation of emotion-cognition interactions. Influences of emotion on cognition have been documented in a wide range of domains, including attention, memory and reasoning (Dolan, 2002). Here we investigated working memory of emotional faces, and thus memory in a specifically social context, because significant heritability estimates have been obtained for both face memory and emotion recognition (Gur, et al., 2007). We were interested in genetic influences on emotional face WM because we had noted considerable interindividual variability of WM performance benefits for happy and angry compared to neutral faces (M. C. Jackson, et al., 2009; M.C. Jackson, Wolf, Johnston, Raymond, & & Linden, 2007; M. Jackson, et al., 2008; Langeslag, et al., 2009). Performance benefits for angry faces were related to enhanced neural processing of angry compared to happy and neutral faces in prefrontal, temporal and subcortical areas (M. Jackson, et al., 2008). Because of dysbindin-1 expression in all of these areas, association of the SNP rs1047631 with differences in dysbindin-1 expression, and dysbindin's role in both dopaminergic (Iizuka, Sei, Weinberger, & Straub, 2007; Kumamoto, et al., 2006) and glutamatergic neurotransmission (Numakawa, et al., 2004; Talbot, et al., 2006; Talbot, et al., 2004), we hypothesized that genotypic differences for SNP rs1047631 in healthy volunteers contribute to individual differences in emotion effects on WM at the neurophysiological and behavioural level.

Materials and methods

Participants

56 participants (31 males, 52 right handed, age 31.8 ± 9.1 years, min 19 max 51 years, all European Caucasians) were recruited from the local community and through the Bangor University participant panel and were paid £25. Participants had no lifetime or family history of any psychiatric or neurological disease and normal or corrected to normal vision. They provided written informed consent prior to participation. The study was approved by the School's ethics committee in Bangor.

Stimuli

Six adult, male, greyscale Ekman face images each displaying neutral, happy and angry expressions were used. Each image covered approximately 1.43° x 1.36°. Scrambled greyscale face images selected at random were displayed to cover the face locations during encoding of fewer than 4 faces.

Working memory task for emotional faces

The behavioural paradigm has been tested in detail in previous studies (M. C. Jackson, et al., 2009; M. Jackson, et al., 2008). In an event-related design (**Figure 1**) the influence of emotional expressions on visual WM capacity for faces and task-related brain activity was investigated through the manipulation of face expression (angry, happy, and neutral) and the number of faces to be remembered (load 1, 2, 3, 4). Each of the 12 conditions consisted of 4 match and 4 non-match trials. Trials were distributed over 4 runs with 48 trials each to minimize fatigue effects. Face expressions and face load varied randomly between trials and type of face expression was kept constant within one trial. Faces were presented at randomly alternating locations in a 2 x 2 matrix in the centre of the screen, and the centre of each image

within the matrix was positioned at a visual angle of approximately 1.27° from fixation to ensure that the face display was foveal. In order to avoid eye movement artefacts, participants were asked to maintain fixation throughout each imaging session. All trials started with fixation towards a central cross on the display which served as baseline. This was followed by two seconds presentation of the memory array, a delay of one second, and the test face, where participants had to indicate a match or non-match response via the respective button. The between trials fixation interval jittered between 4500 - 6000 ms.

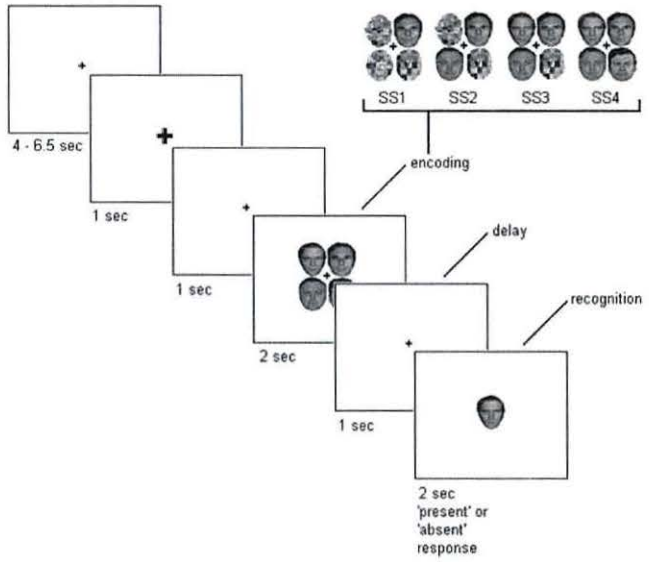

Figure 1. Dynamic of trials and session structure of working memory task for emotional faces.

Acquisition and analysis of behavioural and imaging data

The task was generated and behavioural data recorded with the E-Prime software (Version 1.1, Psychology Software Tools, Inc.). Scanning was performed with a Philips 1.5T MRI whole-body scanner with a SENSE parallel head coil. Blood oxygenation level-dependent images were acquired by using a T2* weighted gradient echo planar sequence (repetition time (TR) = 2000 ms; echo time (TE) = 40 ms; matrix size = 96 × 96; field of view (FOV) =256 ×

256 mm^2; voxel size =3 × 3 × 3 mm^3; 90° flip angle; 20 axial slices; 5 mm slice thickness). The first two volumes of each session were discarded to reduce possible T1 saturation effects. During each of the four working memory sessions 343 volumes were acquired. A high-resolution T1-weighted 3D anatomical MR data set was used for co-registration (TR/TE = 11.5/2.95ms; FA = 8°; coronal slice thickness = 1.3 mm; acquisition matrix 256 × 256; in-plane resolution 1 × 1 mm^2).

Working memory accuracy was assessed by calculating d'prime values (d'prime = z-transformed Hits - z-transformed False Alarms) for each of the 12 conditions and each subject. Working memory capacity for faces was measured by individual Cowan's K Max values for each emotion (Cowan's K Max = maximal K reached for this individual at any array size; Cowan's K values = array size * (Hits – FA)).

Imaging data analysis was performed using the BrainVoyager 1.9.10 software (Braininnovation, Maastricht, The Netherlands). Functional images were co-registered with the structural 3D image, spatially normalized to the Talairach system and resampled at a voxel size of 1 × 1 × 1 mm^3, resulting in 218 z-normalized volume time course files (vtcs), (six runs could not be used because of motion artefacts ; head motion > 3 mm or chance performance; FA mean > 0.5). Functional images were scan time corrected using sinc interpolation, 3D motion corrected using trilinear interpolation, spatially smoothed (8 mm Gaussian kernel), and temporally high pass filtered (3 cycles per time course). The 218 design matrix files (rtcs) for the general linear model (GLM) analysis incorporated predictors for each of the 12 conditions for all correct trials, one separate predictor for all error trials and 6 predictors derived from the head motion correction for each subject. All but the motion predictors were convolved with a two-gamma haemodynamic reference function.

Based on these vtcs and rtcs from all subjects we computed a random-effect general linear model (RFX-GLM) to obtain beta values per subject and condition at each voxel. These were used as dependent variable to compute a second-level RFX-within-subject two-factors

ANOVA with the within subject factors emotion (3 levels) and load (4 levels) to generate functional whole-brain 3D maps for the contrasts angry minus neutral and happy minus neutral faces. In order to reduce the probability of false negatives while still reducing false positives, we corrected for multiple comparisons by using cluster-size thresholding (Forman, et al., 1995; Goebel, Esposito, & Formisano, 2006) for which we set a corrected significance threshold of $p < .05$. Cluster thresholds were set at 200 voxels and calculated using Brainvoyager QX Cluster-level Statistical Threshold estimator based on a Monte Carlo simulation with 1000 iterations. For each of these clusters an RFX-GLM region of interest (ROI) analysis was computed to extract beta values representing the mean activity over the entire cluster for all 12 task conditions (including only correct trials) per subject for subsequent correlation with behavioural data and statistical analysis in combination with the genetic data.

Finally we tested whether activity in regions affected by overall task performance overlapped with activity in regions affected by genotype. Whole brain maps including individual scores for global performance (z-transformed mean of hits across all 12 conditions minus z-transformed mean of false alarms across all 12 conditions) as covariate were computed for both emotion contrasts (angry-neutral and happy-neutral), and correlations between this performance score and the respective contrast were visualised at a threshold of r (54) =.26 (p<.05). Each correlation map was overlaid with the respective original contrast map. For regions with overlapping activity beta values were extracted for subsequent statistical analysis for genotype effects.

Genotyping

Genomic DNA was extracted from venous EDTA blood samples, using Invisorb® Blood Giga Kit (Invitek, Berlin). The DNA sequence fragment containing SNP rs1047631 was PCR-amplified (5'-GGT TTG GCT ACA GTC AGC TCT T-3' and 5'-AGG ACA GCG ACT CTT

AAA TTG G-3', annealing temperature 60°C; 36 cycles, amplification fragments length 444bp). Genotypes were discriminated by digesting PCR-amplified gene products with restriction nuclease BsaA I (New England BioLabs, USA) at 37°C for 4.5 hours. The genotype fragments (*GG* genotype 121bp and 321bp; *AA*-genotype 442bp; *GA* genotype 121bp, 321bp and 442bp) were separated via electrophoresis on a 2% agarose gel supplemented with ethidium bromide (Promega, UK) and visualized under UV-light. The genotyping results for 18% of the samples analysed were replicated with 100% accuracy to ensure high genotype fidelity.

Statistical analysis

a) Analysis of genetic data

Hardy-Weinberg-Equilibrium was checked with χ^2-test (α-level .05; DF = 2), χ^2-test (α-level .05; DF =1) and independent-samples t-test (2-tailed) were used to test whether genotype groups differed on confounding factors.

b) Genotype effects on WM-capacity

We performed independent-samples (*GA* versus *AA*) t-tests (2-tailed) for d'prime mean differences (angry-neutral, happy-neutral, angry-happy and angry&happy-neutral) and maximal Cowan's K values (all 3 emotions) to assess *DTNBP1* genotype effects on working memory accuracy differences (angry-neutral, happy-neutral, angry-happy and angry&happy-neutral) as well as on the individual working memory capacity for each emotion.

c) Correlations between brain activity and WM-performance

Beta value measures (beta means for angry, happy and neutral faces averaged across the four loads and beta mean differences between angry and neutral as well as happy and neutral) from each of the brain regions significantly activated for the angry-neutral and happy-neutral contrasts were tested for correlation (Pearson's correlation coefficient, 2-tailed) with behavioural measures (d'prime mean values for angry, happy and neutral faces averaged

across all loads and the d'prime mean differences between angry or happy and neutral), in order to determine task-performance relevant brain regions. Correlations were used as a filter to select those regions for the analysis of dysbindin-1 genotype effect which were active in relation to working memory performance for angry and/or happy faces.

d) Genotype effects on brain activity

Only brain regions where activity significantly correlated with task-performance were analyzed for genotype effects. Mixed ANOVAs with two within-subjects factors (emotion: angry, happy, neutral and load: 1 to 4) and one between-subjects factor (*DTNBP1* genotype: *GA*, *AA*) were calculated to assess genotype effects on brain activation. We then tested the genotype effect for each emotion (averaged across load) separately and for the difference between angry or happy and neutral using independent-samples t-test (2-tailed).

e) Power calculations

Power calculation were carried out using the DSS Research Statistical Power Calculator software based on the observed means, standard deviations, sample size for an 5% α - level (2-tailed). The probability for not detecting the DTNBP1 genotype effect on WM performance (d'prime) for the difference between happy and neutral faces ($\beta - 1$) was .52. At the neural network level the probability for not detecting the genotype effect ($\beta - 1$) for example in the right occipital cortex was .21 for angry, .18 for happy and .30 for neutral faces.

Results

Dysbindin-1 genotype

The frequency for the G-allele of the *DTNBP1* SNP rs1047631 was 0.12 with the genotypes distributed according to Hardy-Weinberg equilibrium. There were no individuals homozygous for the G-allele. Participants in the *GA* (N = 13) and *AA* (N = 43) groups showed no significant difference of age, years of education, gender or handedness (**Table 1**).

Table 1. Participants with different genotype differed not significantly ($p > .05$) according to gender, handedness or age. Displayed are the number of subjects and the expected numbers (in brackets) in each group and Chi-square values for the categorical variables gender and handedness, and group means and p-value from t-test (2-tailed) for age.

confounding factor		*DTNBP1* GA	*DTNBP1* AA	Pearson Chi-Square or t-Test (DF = 1)	(DF = 54)
gender	male	7 (7.2)	24 (23.8)	.90	
	female	6 (5.8)	19 (19.2)		
handedness	right	12 (12.1)	40 (39.9)	.93	
	left	1 (0.9)	3 (3.1)		
age		$M = 33.69$	$M = 31.28$		
		$SD = 7.91$	$SD = 9.40$		.41

Dysbindin-1 genotype affects working memory performance for happy faces

When we pooled the angry and happy compared to the neutral condition, there was no significant ($p = .44$) effect of the DTNBP1 genotype on WM accuracy (d'prime difference). The difference between angry and happy likewise was not affected significantly ($p = .14$) by the genotype. Both genotype groups showed better WM accuracy for angry compared to neutral faces (d'prime difference angry minus neutral for *GA* group $M = 0.35$, $SE = 0.22$; for *AA* group $M = 0.22$, $SE = 0.10$), but there was no difference of this angry benefit between groups. Conversely, for happy vs. neutral faces only the *GA* group had significantly better WM accuracy (d'prime difference happy minus neutral for *GA* group $M = 0.38$, $SE = 0.19$; for *AA* group $M = -0.02$, $SE = 0.09$). This group difference was significant at $t(54) = 2.08$, $p < .05$, representing a medium effect $r = .27$ (7% of variance explained) of the *DTNBP1* genotype (**Figure 2a**).

The K max, an estimate of WM capacity, was also higher for happy faces in the *GA* group ($M = 2.70$, $SE = 0.18$) than in the *AA* group ($M = 2.29$, $SE = 0.10$), $t(54) = 1.97$, $p = .05$ representing a medium effect ($r = .26$) of genotype on the maximal number of happy faces held in WM (**Figure 2b**).

When we added participant gender as a factor to our analysis of DTNBP1 genotype effects on WM performance (d'prime and Kmax) we found neither an influence of gender nor any interaction between DTNBP1 genotype, gender and type of emotion with all at least $p > .1$.

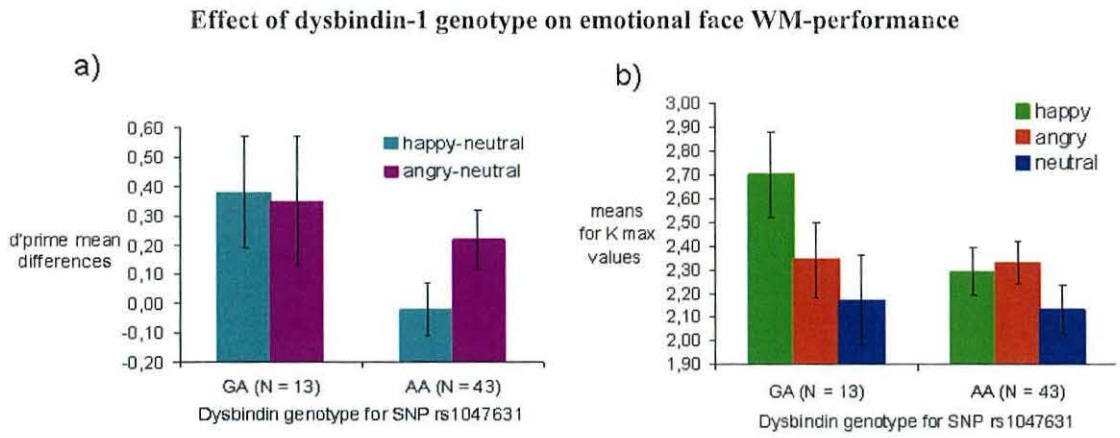

Figure 2. a) The d'prime (WM-accuracy) mean difference between happy and neutral faces was significantly bigger ($p < .05$) in the GA group than AA group. Genotype groups differed not significantly for the d'prime difference between angry and neutral faces. Error bars display standard error of the mean. **b)** The K max mean values (WM-capacity) were higher ($p = .05$) for happy but not for angry or neutral faces in participants with GA- compared to AA-genotype. Error bars display standard error of the mean.

Imaging data

We sought to unravel why working memory performance for happy but not for angry faces was significantly improved in participants heterozygous for the G-allele. First we identified brain regions with significantly higher activity during WM for angry compared to neutral and happy compared to neutral faces, based on the performance benefit for these emotions. Second we tested those brain regions for significant correlations between WM-related activity and WM-accuracy for angry, happy or neutral faces. Third, we analyzed the activity in regions with significant activity-accuracy correlations for modulation by dysbindin-1 genotype.

1. Neural correlates of working memory for angry and happy faces

There was no significant interaction between the factors load and emotion, and we thus report planned whole-brain contrasts (angry-neutral and happy-neutral) with emotions pooled across loads applying a cluster threshold correction for multiple comparisons of 200 voxels at $p <$ .05. Higher activation for angry faces compared to neutral faces was observed in the left and right insula, right superior temporal sulcus (STS), right and left inferior temporal gyrus (ITG),

left and right globus pallidus (GP), right orbital-frontal cortex (OFC), left and right ventrolateral prefrontal cortex (VLPFC), right dorsolateral premotor cortex (DLPC), right middle frontal gyrus (MFG), right caudate nucleus (CN), right amygdala extended, left hippocampus, left and right fusiform face area (FFA), lower part of the right intra-parietal sulcus (IPS), right inferior parietal lobe (IPL), right and left occipital cortex (OC), right and left occipital face area (OFA, (Peelen & Downing, 2005), and left substantia innominata (SI) (**Fig. 3a, Tab. S1a**).

Higher activation for happy compared to neutral faces was observed in the left and right OC, left and right OFA, left insula, left SI, right VLPFC, right and left inferior frontal gyrus, right OFC, right inferior and middle temporal gyrus, right and left amygdala, left FFA, and left entorhinal cortex (**Fig. 3b, Tab. S1b**).

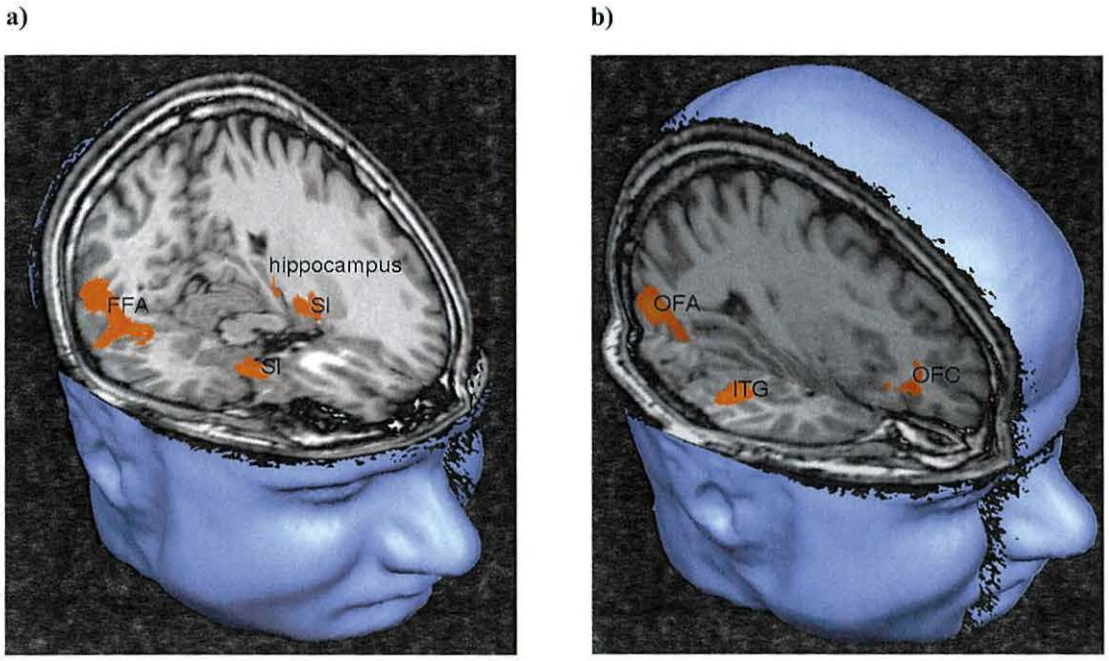

Figure 3. a) Higher activation for angry than neutral faces in the right fusi form face area (FFA), left hippocampus, right and left substantia innominata (IS). **b)** Higher activation for happy than neutral faces in the right occipital face area (OFA), right inferior temporal gyrus (ITG) and right orbital frontal cortex (OFC), $p < .05$ and cluster-threshold 200 voxels.

2. Activity-performance correlations of working memory for angry and happy faces

Increased activity correlated significantly with better WM accuracy in 16 brain regions activated for the angry-neutral contrast and the happy-neutral contrast (**Tab.2**). All regions

with significant activity-accuracy correlations for happy faces showed correlations between mean activity and mean accuracy for happy faces, and additionally for the difference between happy and neutral faces in the STS, ITG and FFA of the right hemisphere. For angry faces, only the right IPL, left OFA and bilateral ITG showed significant correlations between mean activity and mean accuracy, with all remaining activity-accuracy correlations for angry faces referring to the difference between angry and neutral faces. WM accuracy-activity correlations for emotions and emotion contrasts thus differed between brain regions.

Tab.2 Brain regions where activity significantly correlated with behavioural WM-performance.

Brain region	d'prime mean by condition & mean beta values by condition	R^2	p	Brain region	d'prime mean difference between conditions & beta mean difference between conditions	R^2	p
Right FFA	happy	.08	.040	Right amygdala extended	angry & neutral	.09	.027
Right GP	happy	.07	.042	Right CN	angry & neutral	.10	.021
Right IPL	angry	.08	.038	Right FFA	angry & neutral	.23	< .001
	neutral	.10	.016		happy & neutral	.11	.012
Right IPS	happy	.11	.011	Left FFA	angry & neutral	.13	.006
	neutral	.10	.021				
Right ITG	happy	.13	.006	Left hippo-campus	angry & neutral	.08	.030
	angry	.08	.033				
Left ITG	happy	.10	.015	Right IPL	angry & neutral	.24	< .001
	angry	.07	.044				
	neutral	.14	.005				
Right OC	happy	.07	.044	Right ITG	angry & neutral	.07	.049
					happy & neutral	.10	.016
Right OFA	happy	.07	.046	Left OC	angry & neutral	.08	.037
	neutral	.09	.024				
Left OFA	angry	.09	.022	Right OFA	angry & neutral	.14	.005
	happy	.08	.039				
Right OFC	happy	.09	.022	Left OFA	angry & neutral	.10	.019
Right STS	happy	.13	.007	Right STS	angry & neutral	.15	.003
					happy & neutral	.17	.001

3. Effect of dysbindin-1 genotype on task-related brain activity measures

Of the above areas that showed both higher activities for emotional compared to neutral faces and correlations of activation levels with performance, only FFA, ITG, OFC, OC and OFA of the right hemisphere and the left hippocampus showed a significant dysbindin-1 genotype effect. In all brain regions the genotype effect was produced by enhanced activity for the *GA* compared to the *AA* group (**Fig. 4a-f**).

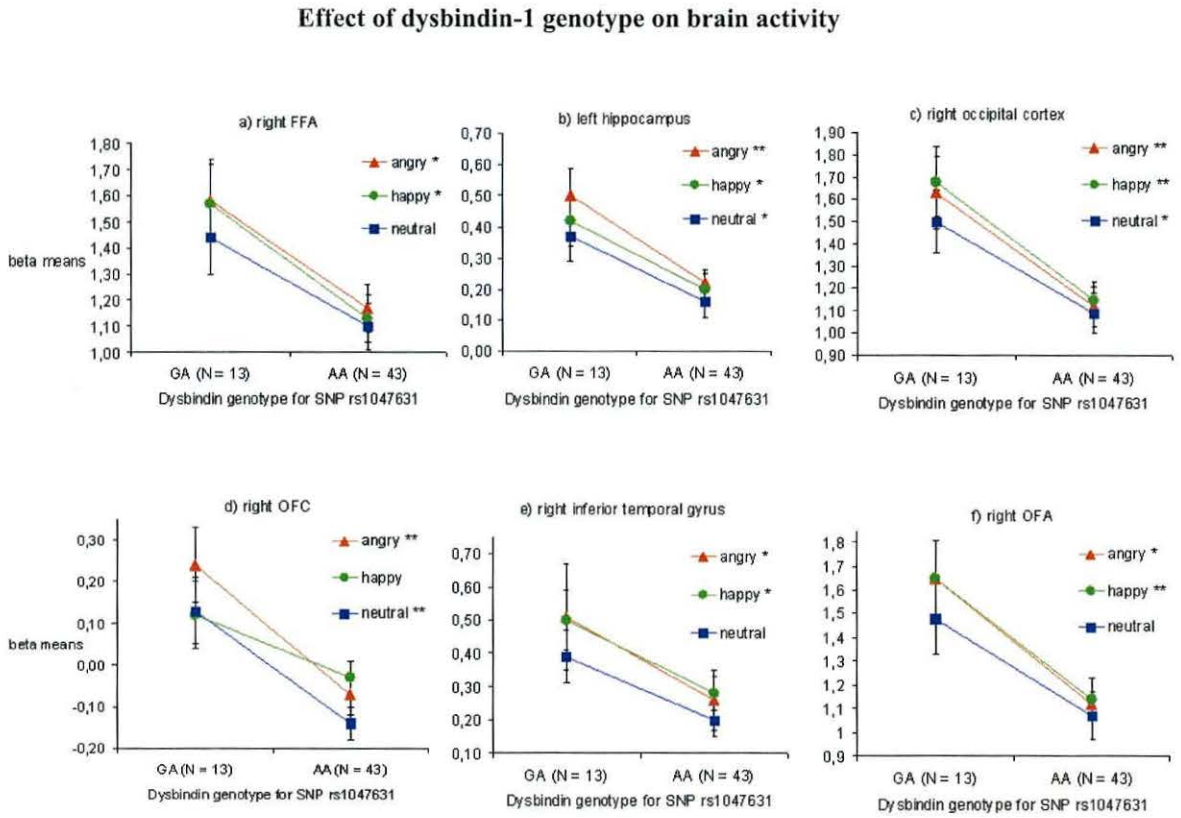

Figure 4. Effect of dysbindin-1 genotype on beta means for angry, happy and neutral faces (* $p < .05$, ** $p < .01$, *** $p < .001$) **a)** the right fusiform face area, **b)** left hippocampus, **c)** right occipital cortex, **d)** right orbital frontal cortex, **e)** right inferior temporal gyrus and **f)** right occipital face area. Error bars display standard error of the mean.

In the left hippocampus **(Fig. 4b, Tab. S2b)** and right OC **(Fig. 4c, Tab. S2c)**, the *GA* group showed significantly higher activity than the *AA* group for all face categories. In the right FFA **(Fig. 4a, Tab. S2a)**, right OFA (**Fig. 4f, Tab. S2f**) and right ITG (**Fig. 4e, Tab. S2e**), activity for angry and happy but not for neutral faces was significantly higher in the *GA* versus *AA*

group. In the right OFC (**Fig. 4d, Tab. S2d**), activity for angry and neutral faces but not for happy faces was significantly enhanced in the *GA* versus *AA* group.

4. Relationship between overall task performance and dysbindin-1 genotype on task-related brain activity

A whole brain correlation analysis between the global performance and brain activity for each emotion contrast (angry-neutral/ happy-neutral) at $p < .05$ and cluster threshold 200 voxels (and even without applying the cluster threshold) revealed no overlap with the respective original emotion contrast maps (**Fig. S1**) except in the right and left inferior frontal sulcus region for the happy-neutral maps. ANOVAs revealed no significant DTNBP1 effect on activity in the right ($p = .49$ and left ($p = .74$) DLPFC in agreement with our initial analysis that revealed no genotype effects in both these regions.

Discussion

We report a dysbindin-1 genotype effect on WM performance for emotional faces that is also reflected in enhanced task-related brain activity. Participants heterozygous for the G-allele (the *GA* group) compared to homozygous A-allele carriers (the *AA* group) for SNP rs1047631 showed better WM accuracy for happy faces compared to neutral faces and also higher individual maximal WM capacity for happy faces. At the neurophysiological level we found enhanced activity for happy faces in the right FFA, left hippocampus, right OC, right OFA and right ITG in the *GA* compared to the *AA* group. The *GA* group also showed increased activity for angry faces in these regions and additionally in the right OFC. Except for the occipital cortex for which expression data is still unavailable, these brain areas match with those where dysbindin-1 mRNA (Bray, et al., 2005; Weickert, et al., 2004) and protein expression have been reported (Talbot, et al., 2006; Talbot, et al., 2004). The G-allele of SNP rs1047631 has been associated with a 17-19% mRNA expression increase in prefrontal and

temporal areas (Bray, et al., 2005; Weickert, et al., 2004). All these brain regions except the right FFA, right OFA and right ITG also showed higher activity for neutral faces in *GA*-genotype carriers. This suggests an effect of the *GA* genotype on WM-related brain activity in regions likely to express dysbindin-1.

Neural correlates of working memory for angry and happy faces:

Irrespective of the genotype effect we identified brain regions with enhanced activity for angry or happy compared to neutral faces to test whether those regions contribute to WM performance for angry or happy compared to neutral faces. Correlations between WM performance and WM-related brain activity were significant in STS, FFA, OFC, OC, OFA, amygdala extended, hippocampus, ITG, GP, IPS, IPL and CN, regions repeatedly reported in fMRI studies of emotional face processing (Sambataro, et al., 2006; M. Williams, McGlone, Abbott, & Mattingley, 2008) and face WM (M.C. Jackson, et al., 2007; LoPresti, et al., 2008; Rissman, Gazzaley, & D'Esposito, 2008). In addition electrophysiological evidence points to face and/or face expression processing neurons in the STS, OFC, FFA, ITG and the amygdala (Rolls, 2007), adding to the plausibility of brain areas with emotion effects in the present study. All significant correlations were positive, linking higher activation with better task performance.

Although the *DTNBP1* genotype affected brain activity for all emotion conditions, at the behavioural level it only showed a significant effect on WM for happy faces. Interestingly in the FFA, ITG, OC and OFA of the right hemisphere, the significant enhancement of activity for happy faces in the GA group compared to the AA group was combined with a positive correlation of performance and activity for happy faces. Conversely, for angry faces we found a correlation between activity and performance and significantly increased activity for angry faces associated with the GA genotype only in the right ITG. The reason for the selective enhancement of WM capacity for happy faces may thus lie in the genotype-

associated increases in activity and the positive effects of increased activity on task performance in these early visual areas for happy faces.

Several previous studies of genotype effects on neural activity have observed activity changes that did not translate into performance differences (Blasi, et al., 2005; Canli, et al., 2005; Schott, et al., 2006). This observation suggests that the small neurochemical changes brought about by most functional polymorphisms need to influence performance-related neural activity in a critical number of regions within the task-related neural network before they will significantly alter behavioural performance.

Link with schizophrenia

The G-allele of SNP rs1047631 is included in a putative protective haplotype for schizophrenia that also comprises the G-allele of marker rs3213207 and T-allele of marker rs760761, which both were shown to be under-transmitted in patients with schizophrenia (Bray, et al., 2005). This haplotype has been strongly associated with high *DTNBP1* expression (Bray, et al., 2005). The combination of the T-allele of SNP rs2619538, and the A-allele of rs3213207 with the A-allele of rs1047631 has been demonstrated to maximize the frequency difference (5.2%) between patients with schizophrenia and healthy controls (Bray, et al., 2005). The relative expression of the A-allele of SNP rs1047631 has been found to be more reduced in the presence than in the absence of this T-A-A risk haplotype (Bray, et al., 2005). Even in the absence of this risk haplotype, interindividual variability of relative DTNBP1 expression has been observed, demonstrating that this risk haplotype can account for some but not all variation in DTNBP1 expression (Bray, et al., 2005). Furthermore the low expression A-allele has been shown to be in phase with several previously identified risk haplotypes (Bray, et al., 2005). The alleles T and A of SNP rs2619538 and rs3213207 from the T-A-A risk haplotype are also included in the C-A-T haplotype associated with schizophrenia (N. Williams, et al., 2004) which has been linked to reduced bilateral occipital

response during low-level visual processing in patients with schizophrenia (Donohoe, et al., 2008). Schizophrenia patients and control participants carrying the T-allele of rs1018381, which is a tagging SNP for another dysbindin-1 haplotype linked to schizophrenia, showed significantly worse general cognitive ability (Burdick, et al., 2006). Interestingly, in this sample the T-allele was in complete linkage disequilibrium with the A-allele of rs1047631, the risk allele of the polymorphism investigated in the present study (Burdick, et al., 2006). Taken together these findings suggest that SNP rs1047631 is probably non-independent of other markers that also index variability in DTNBP1 gene expression, variability at the neurophysiological and the behavioural level, as well as the genetic risk for schizophrenia. Thus, future studies of neural and behavioural effects of DTNBP1 variability should look at the entire haplotypes rather than individual SNPs.

Although the associations between variability in the dysbindin gene and schizophrenia are still tentative, they are interesting in light of the reported reductions of *DTNBP1* mRNA and expression in the substantia nigra, hippocampus and PFC of patients with schizophrenia (Talbot, et al., 2004; Weickert, et al., 2008; Weickert, et al., 2004), which may be related to changes in dopaminergic states of these regions, negative symptoms and cognitive impairments in schizophrenia (Murotani, et al., 2007). Underexpression of dysbindin may thus also contribute to the well-documented deficits in emotion processing in schizophrenia (Sachs, et al., 2004; Tsoi, et al., 2008).

Neurobiological mechanisms for *DTNBP1* effects

How then can changes in *DTNBP1* expression affect neuronal functioning? Up-regulation of *DTNBP1* protein expression in cultured cortical neurons induced expression of the pre-synaptic proteins SNAP25 (SNAP25 is one component of SNARE protein complex, involved in intracellular vesicle trafficking and neurotransmitter release) and synapsin I (synaptic vesicle-associated, cytoskeletal protein) resulting in enhanced exocytotic glutamate

release (Numakawa, et al., 2004). Higher *DTNBP1* expression also promoted neuronal function and survival via the phosphorylation of Akt protein (protein kinase B, PKB) mediated by activation of the phosphatidylinositide 3-kinase (PI3K) pathway. The down-regulation of dysbindin-1 protein resulted in the opposite effects on glutamate release, protein expression and neuronal survival (Numakawa, et al., 2004). In neurons of the midbrain, knockdown of dysbindin-1 increased dopamine release and SNAP25 protein expression, while up-regulation of dysbindin-1 showed no significant effect on SNAP25 protein expression (Kumamoto, et al., 2006).

These combined findings suggest a region and transmitter-system dependent role of *DTNBP1* expression. Thus a critical reduction of *DTNBP1* might reduce glutamatergic as well as dopaminergic signalling and SNAP25 expression in regions such as orbital frontal cortex and hippocampus while increasing dopaminergic signalling and SNAP25 expression in the midbrain. With respect to our results in healthy volunteers this suggests that the reduced task-related activity that we observed in regions such as hippocampus and orbital-frontal cortex in carriers of the genotype associated with reduced *DTNBP1* expression may be linked to reduced and/ or less efficient glutamatergic and dopaminergic signalling in these areas. Considering the reciprocal connections between these regions (Roberts, et al., 2007), dopamine signalling in orbital frontal-cortex could affect hippocampal-prefrontal synaptic transmission and dopaminergic neurons in midbrain could be modulated by PFC and hippocampus.

Nevertheless the high percentage of carriers with the dysbindin-1 genotype associated with low expression suggests some advantage of reduced dysbindin-1 levels. These may be linked to its role as activator of the PI3K-PKB pathway with ensuing effects on cell growth, cell division, cell differentiation, cell migration, and cell survival (Kalkman, 2006).

Investigation of genetically-driven interindividual variability in cognitive functions with genetic imaging – potentials and limitations:

Genetic imaging holds the potential to detect genetic effects that influence interindividual differences at the neural network level. It is encouraging that despite the generally small size of genetic effects we found statistically significant associations between a single marker for variability in the dysbindin-1 gene, brain activity and performance measures of a complex WM task for emotional faces. The size of our sample was large enough to detect significant effects at both behavioural and neural network level. The power to detect the DTNBP1 genotype effect on WM performance (d'prime) for the difference between happy and neutral was 48.1%. At the neural network level power to detect the genotype effect for example in the right occipital cortex was 79.2% for angry, 82.4% for happy and 69.7% for neutral, which conforms to suggestions that brain activation measures are more sensitive to gene effects than behavioural measures. The effect sizes are comparable to previous genetic imaging work (Egan, et al., 2003) and a single variant in a single gene is certainly at best a small contributor to the overall interindividual variability in neurophysiological and behavioural measures of a complex trait (Canli & Lesch, 2007). Cognitive traits are modulated by multiple interacting genetic (Butcher, Davis, Craig, & Plomin, 2008), epigenetic (Tsankova, Renthal, Kumar, & Nestler, 2007) and environmental factors (Fish, et al., 2004). Indeed interindividual variability in the relative allelic expression for SNP rs1047631 has been shown, indicating additional cis/trans-acting, epigenetic or environmental influences (N. Bray, et al., 2003; Bray, et al., 2005) on the regulation of the turnover, translation and subcellular localization of dysbindin-1 mRNA. We were particularly interested in SNPs within 3'UTRs because of their potential significance for gene regulation by microRNAs, as assumed for SNP rs1047631 (Luciano, et al., 2009). The translational repression of synaptic proteins by miRNAs has been shown to regulate dendritic growth (Klein, et al., 2007; Schratt, et al., 2006; Wayman, Davare, et al., 2008). In this way changes in regulative mRNA sequences could mediate genetically-driven

neurophysiological changes with effects on cognitive functions as well as being a target of neuronal activity-dependent regulators with effects on gene expression. Genetic imaging can contribute to our understanding of the functions of non-coding sequences by investigating the effects of their variations on complex traits like cognition. However, the conclusions of this study, like of any genetic imaging study, would be strengthened by replication in an independent sample.

The genotype selected for the present study may be paradigmatic of a new trend in the investigation of gene regulation, especially the role of regulative non-coding sequences, and their influence on interindividual differences in complex cognitive traits. Our results suggest that variability in a non-coding sequence of *DTNBP1* contributes to individual differences in emotional working memory and together with previous findings support a role of dysbindin-1 in enhancing synaptic function.

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Competing interest statement

The authors declare that they have no competing financial interests.

For supplementary information please refer to the supplementary materials for experimental chapter I.

Experimental Chapter II

Compensatory network activity supports working memory accuracy in patients with schizophrenia.

This chapter has been submitted at Neuropsychobiology under the same title and contributing authors as indicated below.

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Abstract

Dysfunctional working memory (WM) has been recognized as one of the most consistent deficits in schizophrenia. Studies that investigated the neural correlates of WM-related pathology by comparing patients with schizophrenia and control participants have produced controversial results, reporting task-related hyper-or hypoactivity in fronto-parietal networks. We addressed this question by comparing BOLD-signals for accurate responses during a WM task for emotional faces between a homogenous group of high performing patients and a control group. Our results confirm previous findings of left prefrontal hyperactivity as compensatory adaptation for hypoactivity in right prefrontal cortex to support WM performance. We also extend previous work by reporting enhanced activity in higher visual areas of patients during encoding and maintenance. We integrate our findings and those of the literature into a model where preserved visual cognition in high-functioning patients with hypofrontality is explained by compensation through contralateral homologue areas combined with enhanced recruitment of sensory areas.

Introduction

Schizophrenia is a heterogenous psychiatric disorder reflected in its diversity of symptoms, severity, course and cognitive deficits and it appears to involve the combined effects of multiple genetic, epigenetic and environmental risk factors. Among the cognitive functions frequently affected in schizophrenia, working memory (WM) has been recognized as one of the most consistent deficits (Forbes, Carrick, McIntosh, & Lawrie, 2008; Lee & Park, 2005), that may appear even before the onset of the disorder (Eastvold, Heaton, & Cadenhead, 2007; Hambrecht, et al., 2002) and can be present in first-degree relatives of patients with schizophrenia (Heydebrand, 2006; Park, et al., 1995). Reduced working memory accuracy for face identity and emotional face expressions has been observed in patients with schizophrenia compared to healthy participants (Y. Chen, Norton, McBain, Ongur, & Heckers, 2009; Gooding & Tallent, 2004). Significant heritability estimates have been obtained for accuracy of facial memory and emotion processing (Gur, et al., 2007). Unaffected twins of schizophrenia patients showed BOLD-activation within prefrontal and parietal regions and performance intermediate to their affected siblings and healthy controls during a WM task (K. Karlsgodt, et al., 2007). Besides differences between patients and controls observed at the neural network level, changes at the cellular, sub-cellular (Akbarian, Kim, et al., 1996; Arnold, et al., 1997; Arnold, Talbot, & Hahn, 2005; Honer & Young, 2004; Selemon, Rajkowska, & Goldman-Rakic, 1995) and gene expression level (Mirnics, Middleton, Marquez, Lewis, & Levitt, 2000) in prefrontal and temporal regions have been indicated by schizophrenia post-mortem studies.

There is an ongoing debate (Barch, 2005; Honey & Fletcher, 2006; Manoach, 2003) about whether pathological changes are reflected in alterations of the BOLD-response in frontoparietal working memory networks (D. Linden, 2007). Against this, it has been argued that activity differences between groups are confounded by differences in task performance

and other factors such as level of education. Recent studies that addressed this issue by matching groups on task performance reported WM performance-dependent (Perlstein, Carter, Noll, & Cohen, 2001) and -independent (Thermenos, et al., 2005) activity differences between patients and controls in WM-related regions. We investigated whether emotional face WM-related neural network activity differs between high-performing patients with schizophrenia and healthy participants. In particular we wanted to probe whether activity differences between groups in disease-associated areas (e.g. PFC) would persist under these conditions. For this reason we included only clinically stable patients with at most mild cognitive impairments, good task performance, and matched patients with controls for additional confounding factors. Our results revealed a compensatory network that supports WM performance in patients with schizophrenia.

Experimental Procedures

Participants

10 outpatients and two inpatients diagnosed with schizophrenia spectrum disorder (1 schizoaffective, 11 paranoid schizophrenia) according to *DSM-IV* criteria were assessed with the Structured Clinical Interview for *DSM-IV* and recruited by a psychiatrist (S.L.) from the Psychiatry Unit at Gwynedd Hospital. Current clinical symptoms were evaluated with the Positive and Negative Symptoms Scales (Kay, 1986). An equal number of healthy volunteers matched for gender, handedness, ethnicity, age and education were selected from a large control data sample for the same fMRI paradigm (C. Wolf, et al., 2009). Control participants had no lifetime or family history of psychiatric or neurological disease. Patients and controls had normal or corrected to normal vision. They provided written informed consent prior to participation and were paid £25. The study was approved by the ethics committees at the School of Psychology, Bangor University and at the North Wales NHS-Trust.

Stimuli

Six adult, male, greyscale face images each displaying neutral, happy and angry expressions were used (Ekman, 1976). Each image covered approximately 1.43° x 1.36°. Scrambled greyscale face images selected at random were displayed to cover the face locations during encoding of fewer than 4 faces.

Working memory task for emotional faces

In an event-related design (**Figure 1**) we investigated visual working memory for emotional faces and task-related brain activity through the manipulation of face expression (angry, happy, and neutral) and the number of faces to be remembered (load 1, 2, 3, 4). Each of the 12 conditions consisted of 4 match and 4 non-match trials. Trials were distributed over 4 runs with 48 trials each to minimize fatigue effects. Face expressions and number of faces varied randomly between trials and type of face expression was kept constant within one trial. Faces were presented at randomly alternating locations in a 2 x 2 matrix in the centre of the screen, and the centre of each image within the matrix was positioned at a visual angle of approximately 1.27° from fixation to ensure that the face display was foveal. In order to avoid eye movement artefacts, participants were asked to maintain fixation throughout each imaging session. All trials started with fixation towards a central cross on the display which served as baseline. This was followed by two seconds presentation of the memory array, a delay of one second, and the test face, where participants had to indicate a match or non-match response via the respective button. The between trials fixation interval jittered between 4500 - 6000 ms.

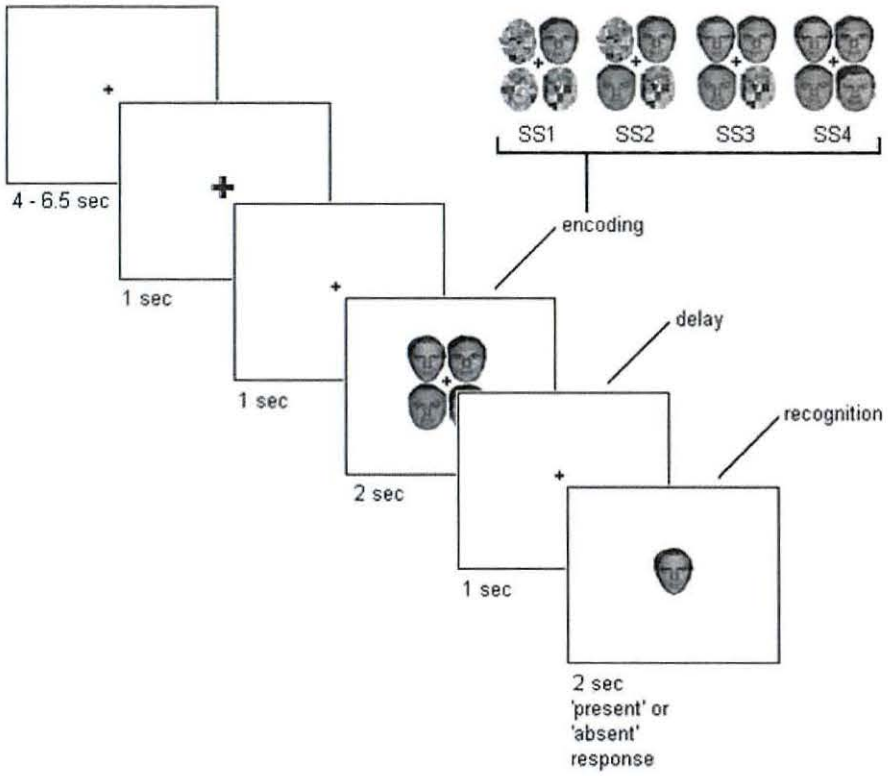


Figure 1. Dynamic of trials and session structure of working memory task for emotional faces.

Acquisition and analysis of behavioural and imaging data

The task was generated and behavioural data recorded with the E-Prime software (Version 1.1; Schneider, Eshman, & Zuccolotto, 2002). Scanning was performed with a Philips 1.5T MRI whole-body scanner with a SENSE parallel head coil. Blood oxygenation level-dependent images were acquired by using a T2* weighted gradient echo planar sequence (TR = 2000 ms; TE = 40 ms; matrix size = 96 x 96; FOV =256 x 256 mm^2; voxel size =3 x 3 x 3 mm^3; 90° flip angle; 20 axial slices; 5 mm slice thickness). The first two volumes of each session were discarded to reduce possible T1 saturation effects. During each of the four working memory sessions 343 volumes were acquired. For the co-registration with functional images one high resolution T1-weighted three-dimensional (3D) volume was acquired.

Working memory accuracy was assessed by calculating d'prime values (d'prime = z-transformed Hits - z-transformed False Alarms) for each of the 12 conditions. Working

memory capacity for faces was measured by individual Cowan's K Max values for each emotion (Cowan's K Max = maximal K reached for this individual at any array size; Cowan's K values = array size * (Hits – FA))(Cowan, 2001).

Imaging data analysis was performed using the BrainVoyager 1.9.10 software (Braininnovation, Maastricht, The Netherlands). Functional images were co-registered with the structural 3D image and spatially normalized to the Talairach system (Talairach & Tournoux, 1988), resulting in 56 z-normalized volume time course files (vtcs), (eight runs could not be used because of motion artefacts or chance performance). Functional images were scan time corrected using sinc interpolation, 3D motion corrected using trilinear interpolation, spatially smoothed (8 mm Gaussian kernel), and temporally high pass filtered (3 cycles per time course). The general linear model (GLM) of the experiment was computed with predictors for each of the 12 conditions for all correct trials, one separate predictor for all error trials and 6 predictors derived from the head motion correction for each subject. All but the motion predictors were convolved with a two-gamma haemodynamic reference function. We computed a random-effect (RFX-GLM), to obtain beta values per subject and condition at each voxel. These were used as dependent variable to compute a second-level RFX- mixed 3 factors ANOVA with the within subject factors emotion (3 levels), load (4 levels) and the between subject factor group (2 levels) to generate functional whole-brain 3D maps for the main effect of group, the group x emotion interaction and the contrast load 4 minus 1. Clusters of activation were thresholded at $p < .01$ for the main effect of group in order to minimise false positive effects. The interaction between group x emotion and the contrast load 4 minus 1 were thresholded at $p < .05$ significance level. The cluster thresholds were calculated with Brainvoyager QX Cluster-level Statistical Threshold estimator to correct for multiple comparisons. For each of the obtained clusters an RFX-GLM region of interest (ROI) analysis was computed to extract beta values representing the mean activity over the

entire cluster for all 12 task conditions (including only correct trials) per subject for extended statistical analysis.

Statistical analysis

a) Matching of patients and controls

Independent-samples t-tests were used to assess whether controls and patients differed according to age and education.

b) Group effects on WM-performance

Mixed ANOVA (between subject factor: group (controls, patients); within subject factors: emotion (angry, happy, neutral) and load (1-4)) was used to test the effect of emotion, load, group and possible interactions on accuracy of working memory for emotional faces. Independent-samples t-test was calculated to test for a group effect on load 4 (averaged across emotions). We performed another mixed ANOVA (between subject factor: group (controls, patients); within subject factor maximal Cowan's K values (all 3 emotions) to assess group effects on the individual working memory capacity for each emotion.

c) Group effects on brain activity

Mixed ANOVAs with two within-subjects factors (emotion: angry, happy, neutral and load: 1 to 4) and one between-subjects factor (group: controls, patients) were calculated to specify the strength of effects on brain activation for each cluster. We then tested the group and load effect on beta means for each load (averaged across emotion) using mixed ANOVAs with the within-subjects factor (load: 1 to 4) and one between-subjects factor (group: controls, patients). Group effects on beta means for each load averaged across emotions were analysed with 2-tailed independent-sample t-tests to identify at which loads groups differed. For the interaction between group and emotion, group effects on beta mean values for each emotion averaged across loads were analysed with 2-tailed independent-samples t-test to analyse how groups differed for each emotion. We also used 2-tailed independent-samples t-test to

compare between groups the % BOLD-signal change averaged across all 12 conditions for each time point. All t-test results were Bonferroni corrected.

Results

Behavioural data

Data from four patients (2 inpatients) with schizophrenia had to be excluded due to head movement artefacts and/or chance task performance. The clinical parameters for the remaining patients and matching details for patients and controls are shown in **Tab.1-2**.

Patients with schizophrenia showed no significant performance deficits of working memory for emotional faces compared to healthy volunteers.

The mixed ANOVA (between subject factor: group (controls, patients); within subject factors: emotion (angry, happy, neutral) and load (1-4)) for mean accuracy (d'prime) of working memory for emotional faces comparing controls and patients revealed a main effect of load F (3, 42) = 84.19, $p < .001$ (**Fig.2**) but no effects of group or emotion and no 2- or 3-way interaction ($p > .05$).

Tab.1 Control-Patient matching parameters

	confounding factors							
group	gender		handedness		ethnicity		age (years)	education (years)
	male	female	right	left	UK	Wales	$t(14) = 0.15$	$t(14) = 1.76$
Controls	6	2	7	1	4	4	$M = 27.63$; $SD = 7.93$	$M = 14.25$; $SD = 2.19$
Patients	6	2	7	1	5	3	$M = 27.00$; $SD = 9.20$	$M = 11.75$; $SD = 3.37$

Tab.2 Assessment of patients with schizophrenia

Clinical characteristics	N = 8 Mean (SEM)
Illness duration in years	4.9 (1.8)
Illness onset age in years	22.1 (2.0)
Total PANSS score	61.1 (4.0)
Negative Factor	15.3 (1.8)
Positive Factor	15.5 (0.8)
General Factor	30.4 (2.3)
Cognitive Factor	7.8 (0.6)
pre-morbid IQ (NART)	107.1 (3.7)
Chlorpromazine equivalents in mg/d	256 (42.3)

*Total PANSS score range 30 (no symptoms) – 210; negative and positive factor range 7 – 49; general factor range 16 – 112; cognitive factor range 6 – 28

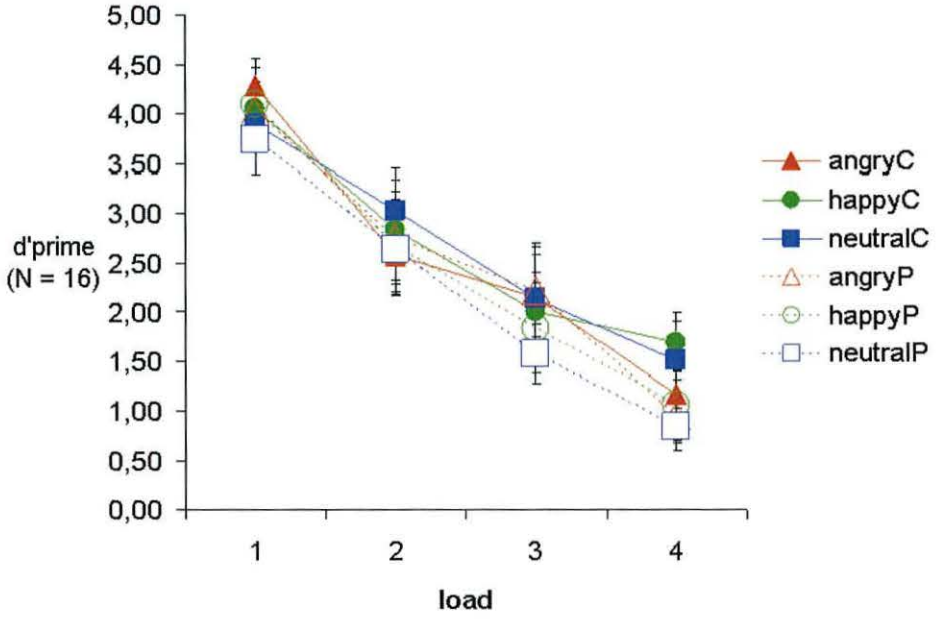


Fig.2 Comparison of d'prime (WM-accuracy) means for each emotion (angry, happy, and neutral) at each load (1-4) between controls (C) and patients with schizophrenia (P) showed no significant differences ($p > .05$). WM-accuracy sig. ($p < .001$) decreased with increasing load. Error bars show the +/-SEM.

The mixed ANOVA (between subject factor: group (controls, patients); within subject factor: emotion (angry, happy, neutral) for K max values (WM-capacity) comparing controls and patients revealed only non-significant ($p > .05$) results for main effects and the interaction (**Fig.3**).

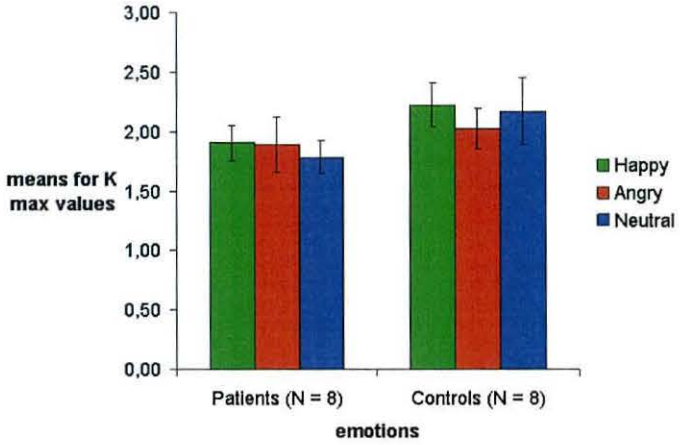


Fig.3 Comparison of K max mean values (WM-capacity) for happy, angry and neutral faces between patients with schizophrenia and controls showed no significant differences. There were no sig. differences between WM-capacities for different emotional faces. Error bars show the +/-SEM.

Imaging data

Only correct trials were included in the analysis of BOLD-response to compare WM accuracy-related areas between patients and controls. There was a significant interaction between emotion and group in the right VLPFC (**Fig.4, Suppl. Tab.3**). This effect was driven by lower activity for neutral faces in patients with schizophrenia compared with control participants.

We found a main effect for group (**Fig.5a & 6, Suppl. Tab.1**) in the left occipital-temporal cortex (OTC) and lateral PFC (driven by higher activation for patients), and right LPFC and MPFC (driven by higher activation in controls). Post-hoc tests revealed that this main effect of group on beta means for load was driven by sig. increased activity in patients compared to controls at load 2 in the left OTC ($p < .01$, Bonferroni corrected), and LPFC ($p < .05$, Bonferroni corrected). The main effect of group was driven by sig. lower activity in patients compared to controls at load 3 ($p < .05$, Bonferroni corrected) in the MPFC ($p < .05$, Bonferroni corrected) and right LPFC ($p < .01$, Bonferroni corrected). The MPFC also showed a significant effect of load, as did right and left parietal cortex (**Fig.6, Suppl. Tab.2**).

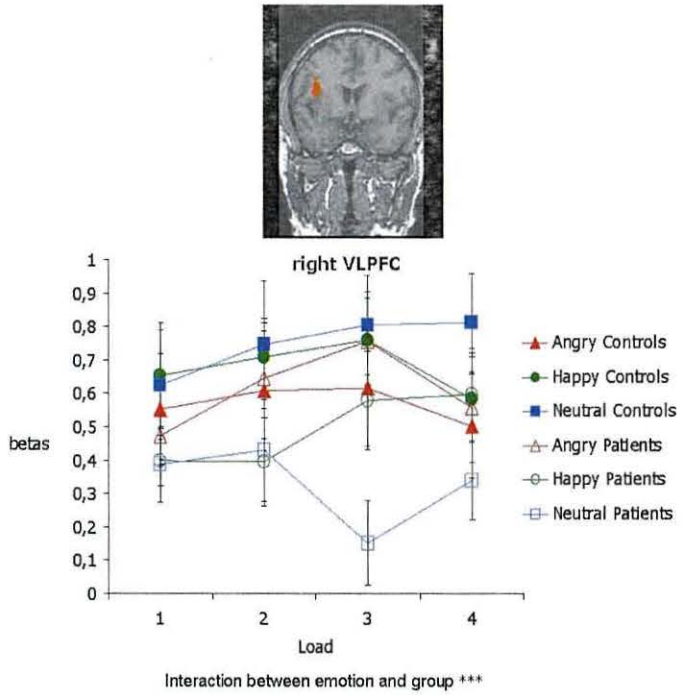
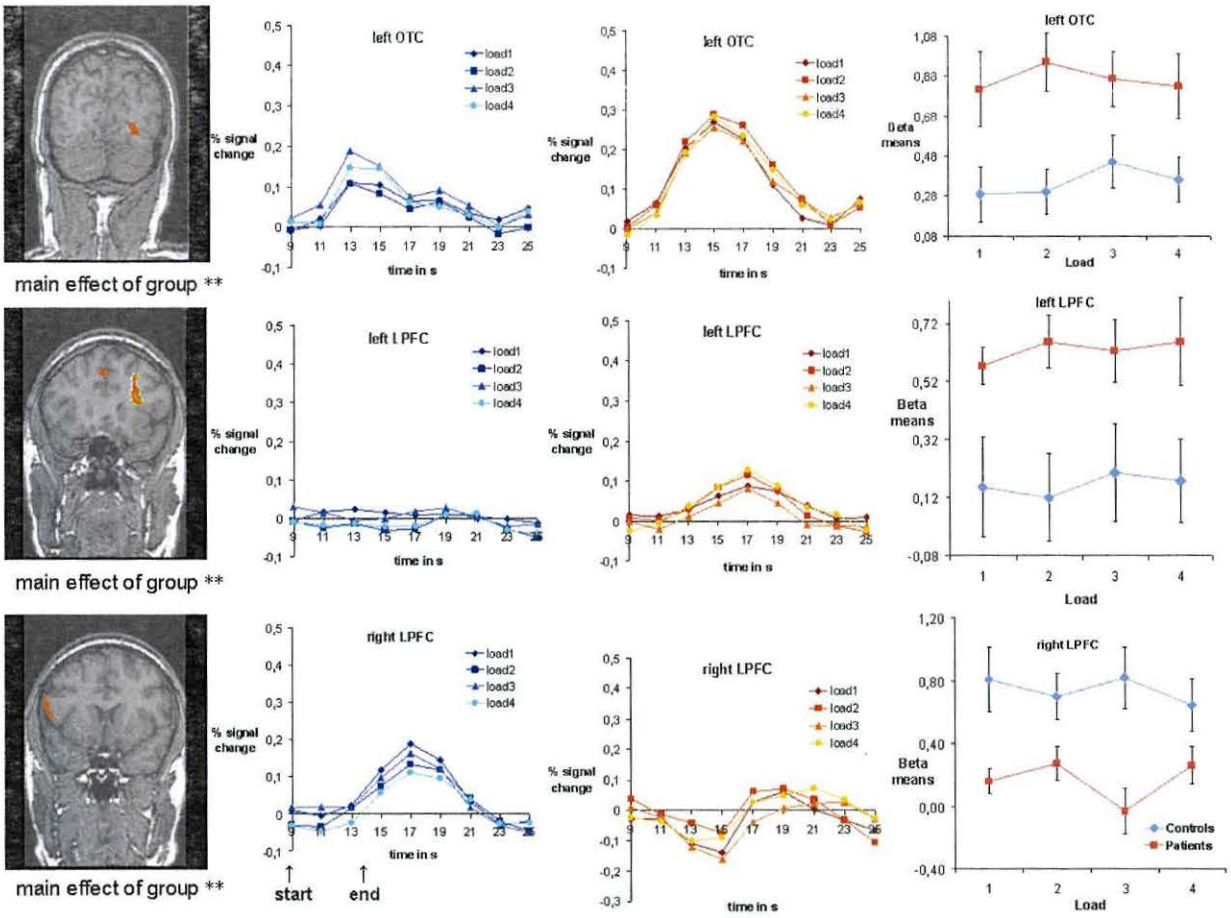


Fig.4 The location of the ROI cluster for the emotion and group interaction ($p < .05$ and cluster threshold 1500 voxels) and beta values for each emotion at each load are shown. Beta mean values for each emotion averaged across loads revealed that this interaction was driven by sig. ($p < .05$, Bonferroni corrected) lower activity for neutral faces in patients compared to controls. Error bars show the +/-SEM.

Event-related averaging showed the maximal BOLD-signal peak 8 seconds after the onset of encoding in the right LPFC in controls and in the left LPFC in patients while there was neither a clear peak response in the right LPFC in patients nor in the left LPFC in controls (**Fig.5a**). In the left OTC patients showed the maximum BOLD-signal 6 seconds after encoding onset while controls showed an earlier and smaller peak after 4 seconds (**Fig.6**). In all load-sensitive areas both groups showed BOLD-signal peaks 8 seconds after the onset of encoding except for the right parietal cortex in controls where BOLD-signal peaked 6 seconds after onset of encoding (**Fig.6**).



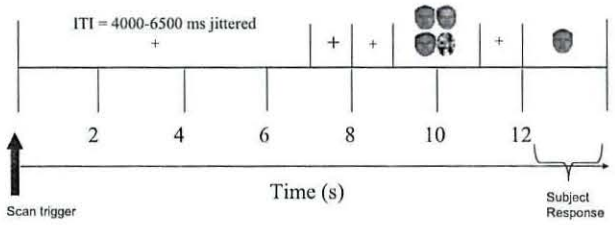


Fig.5a The location of the ROI clusters for the main effect of group ($p < .01$ and cluster threshold 200 voxels), percentage BOLD-signal change mean values (arrows indicate timing of single-trial event) and beta mean values averaged for each load across emotions are shown. Beta means for load were sig. ($p < .01$) higher in patients with schizophrenia compared to control participants in the left occipital-temporal cortex and left lateral PFC. Beta means for load were sig. ($p < .01$) lower in patients compared to controls in the right lateral PFC. Error bars show the +/-SEM.

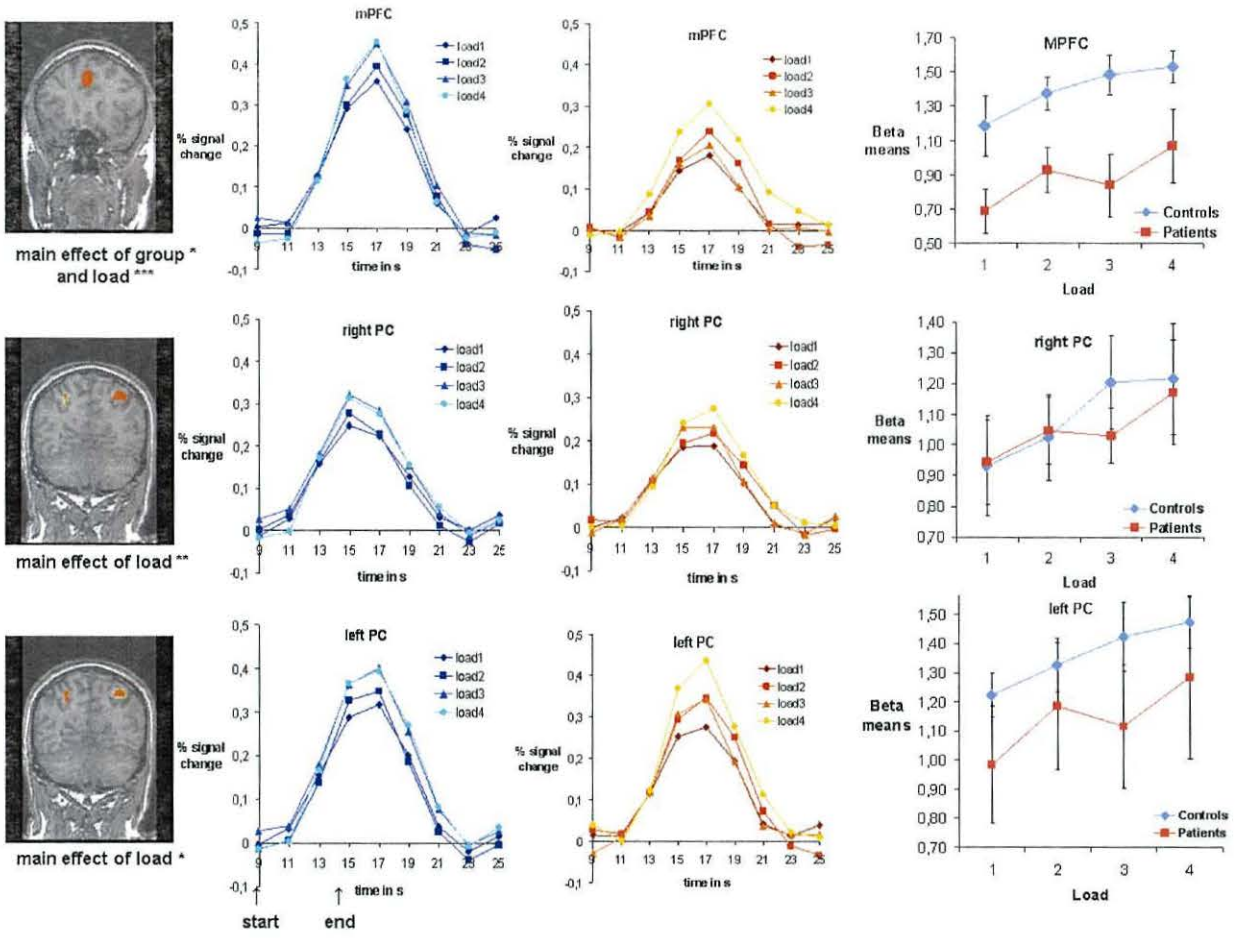


Fig.6 The location of the ROI clusters for the contrast load 4 minus 1 ($p < .05$ and cluster threshold 500 voxels), percentage BOLD-signal change mean values and beta mean values averaged for each load across emotions are shown. Beta means for load increased with increasing load in the right ($p < .01$) and left ($p < .05$) parietal cortex and in the MPFC ($p < .001$). Additionally in the MPFC, beta means for load were sig. lower ($p < .05$) in patients with schizophrenia compared to control participants. Error bars show the +/-SEM.

Activity in the OTC (**Fig.5b, Tab.3a**) differed less between patients and controls in the early phase of encoding (reflected in the time point 13, thus 4 seconds after onset of sample presentation), than during the later stages of the task (most significant differences at time point 17). In the left LPFC (**Fig.5b, Tab.3b**) activity differed between patients and controls solely during the later stages of the task (most significant differences at time point 17).

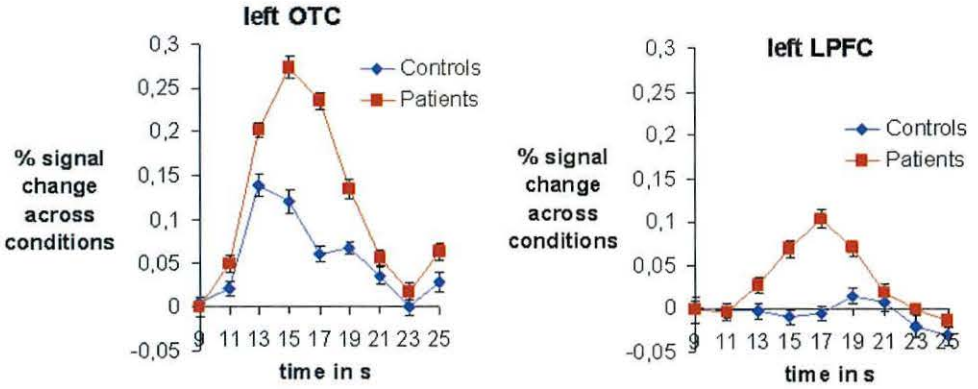


Fig.5b Comparison of percentage signal change means (across all conditions) between groups for each time point in the left OTC and LPFC revealed significant ($p < .001$, Bonferroni corrected) group differences with the maximal difference at 17 seconds. Note that the difference in the left OTC started to become significant at 13s (thus, 4 seconds after onset of the sample array, reflecting the haemodynamic delay of first-pass neural processing) and in the left LPFC 2 seconds later at 15s.

Tab.3 Comparison of % BOLD-signal change means across 12 conditions between groups at each time point

time	left OTC					left LPFC				
points in	Controls		Patients			Controls		Patients		
seconds	*M*	*SD*	*M*	*SD*	*t*(22)	*M*	*SD*	*M*	*SD*	*t*(22)
9	0.00	0.02	0.00	0.04	.29	0.00	0.03	-0.00	0.05	0.20
11	0.02	0.03	0.05	0.03	-2.23	-0.00	0.03	-0.00	0.03	0.11
13	0.14	0.04	0.20	0.03	-4.37***	-0.00	0.03	0.03	0.03	-2.48
15	0.12	0.04	0.27	0.04	-8.63***	-0.01	0.03	0.07	0.03	-6.12***
17	0.06	0.03	0.24	0.03	-14.9***	-0.01	0.03	0.10	0.04	-8.51***
19	0.07	0.02	0.13	0.04	-5.18***	0.02	0.03	0.07	0.03	-4.67***
21	0.04	0.03	0.06	0.03	-1.68	0.01	0.04	0.02	0.04	-0.73
23	-0.00	0.03	0.02	0.03	-1.46	-0.02	0.04	-0.00	0.02	-1.47
25	0.03	0.04	0.06	0.03	-2.55	-0.03	0.04	-0.01	0.02	-1.22

*** $p < .001$ (Bonferroni corrected)

Discussion

Compensatory network supports WM accuracy in patients with schizophrenia

Patients with schizophrenia compared to control participants showed decreased activity in the right lateral and load sensitive medial prefrontal cortex. This was contrasted by left lateralized hyperactivity in the lateral-prefrontal and the occipital-temporal region in patients compared to controls. Activation of the right lateral PFC and in particular right ventrolateral PFC for face WM has been described for healthy populations (Gray, Braver, & Raichle, 2002; M. Jackson, et al., 2008; Rama, et al., 2004; Rama, Sala, Gillen, Pekar, & Courtney, 2001). Activation of the left PFC has been shown to support task performance with increasing WM load in healthy volunteers (Mayer, et al., 2007). Dysfunction of the right LPFC in patients might thus be compensated through the recruitment of the left LPFC to support WM capacity. Activation of the left LPFC in patients could also reflect the use of verbal encoding for which left lateralisation has been shown (Gabrieli, Poldrack, & Desmond, 1998). Hyperactivity of the occipital-temporal cortex in patients compared to controls could indicate enhanced encoding and maintenance during WM. Both areas have been shown to be activated for correct versus incorrect responses during encoding and maintenance (Pessoa, et al., 2002). Independent of activity during encoding increased BOLD-activity during maintenance was found to significantly predict correct WM performance in several regions including the left occipital, parietal and lateral prefrontal cortex (Pessoa, et al., 2002). Our findings are thus consistent with the evidence that WM involves the interaction between LPFC, temporal and occipital cortex (Curtis & D'Esposito, 2003; Fuster, 2001) and that increased activity within this network correlates with WM accuracy.

Controls showed a normal pattern of initial posterior activation in the left OTC, which was followed by right prefrontal activation with a lag of ca. two seconds. This is a common finding of fMRI studies of WM (Mayer, et al., 2007) and may correspond to the transfer of

information from sensory to prefrontal areas and formation of more stable, abstract representations (D. Linden, 2007). Increased activation of the left prefrontal region during the later stages of the task in patients is comparable to the onset of increased activity in the right LPFC in controls. Conversely, patients showed increased and more sustained activity in the OTC compared to controls, starting during the early stages of the task and spanning the maintenance phase, which further supports our interpretation of compensatory posterior activation in this group. Patients' strategy may rely on a more immediate visual representation, conforming to their reports of more vivid mental imagery (Sack, van de Ven, Etschenberg, Schatz, & Linden, 2005). Similar compensatory mechanisms involving activation of higher visual areas supporting configural processing of complex objects have been reported in patients with Alzheimer's disease (Prvulovic, et al., 2002).

Presumably, patients achieved similar performance to controls because of increased activity in the left lateral PFC and occipital-temporal region to compensate insufficient support by the right lateral and medial prefrontal regions. We observed an emotion-specific decreased WM-related activity for neutral faces in patients compared to controls in the left LFPC, which may indicate that patients need more salient (emotional) stimuli to activate this area to the same degree as controls.

Similar emotional face WM performance in patients and controls

WM accuracy decreased significantly with increasing face load in both groups. This is consistent with our previous finding of an effect of load on emotional face WM in healthy volunteers (M. Jackson, et al., 2008). In contrast to our previous study we did not find a significant effect of emotion on WM accuracy or capacity, which is likely owed to the small sample size. There were no significant WM performance differences between patients with schizophrenia and healthy participants, which are in keeping with the behavioural results of (Quintana, et al., 2003). However, it seems to be at odds with the majority of studies with

larger sample size, which have reported WM performance deficits for a variety of tasks and stimuli (Fleming, Goldberg, Gold, & Weinberger, 1995; Forbes, et al., 2008; Lee & Park, 2005; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997; Weinberger & Cermak, 1973). Because of the relatively low power of this study we cannot infer that patients generally do not show a WM deficit (with an effect size for the group difference of $r_{group} = 0.16$ [estimated based on the present data] we would have needed 103 subjects for each group to have 80% power). However, our group of patients only showed a very subtle, if any, performance deficit and is thus interesting for a study of compensatory mechanisms. Moreover, most of our patients were stable outpatients under treatment at the time of their participation, had a pre-morbid IQ above 100 and a PANSS Cognitive Factor below 8 (**Tab.2**), indicating low cognitive deficit. They thus represent a relatively homogenous and high functioning subgroup of patients with schizophrenia. Except one patient who had only 5 years of education all patients had a minimum of 10 years of education. Indeed it appears very complicated to find control participants with less than 10 years of education as none of our 56 controls had less than 10 years of education. Only 4 out of 56 participants had 10 years of education comprising 3 women. Our patients sample included only 2 women with at least 14 years of education. Thus matching for education would have compromised not only matching for age and ethnicity but also gender. Also we would argue that the difference in years of education between controls and patients (which was not significant $p = .1$) would have been of concern in case of significant performance differences between groups which we did not detect. However because significance tests do not test for false negatives, which would have been required in this case but is not possible we admit that matching between patients and controls for years of education was not perfect. It is also known that education of patients is influenced by the course of the illness (Keefe, Eesley, & Poe, 2005) thus it may have been more appropriate to instead match for parental education.

Several previous studies have attempted to match the performance of patients and controls through comparison of activity at lower WM loads in patients with higher WM loads in controls or by exclusion of incorrect trials from the analysis (Manoach, et al., 2000; Perlstein, et al., 2001; Thermenos, et al., 2005; Walter, Vasic, Hose, Spitzer, & Wolf, 2007). However, their findings have remained controversial, providing evidence both for and against performance-dependent activity differences between groups in the right PFC. We present evidence for a hemispheric dissociation of deficit (right LPFC) and compensatory (left LPFC) mechanisms supporting successful WM performance in schizophrenia. We thus corroborate the compensatory activation of the left LPFC reported by (K. H. Karlsgodt, et al., 2009; Manoach, et al., 2000; Quintana, et al., 2003). A longitudinal study found WM accuracy differences between patients and controls at the beginning but not after several weeks of clinical intervention (R. C. Wolf, et al., 2007). This improvement of WM accuracy was associated with enhanced activation within frontal-temporal regions (R. C. Wolf, et al., 2007). Karlsgodt et al., 2009 suggested that the degree of hyperfrontality could indicate the ability for compensatory adaptations in the high performing patients.

Outlook: can we "train" compensatory networks?

Because activity within occipital, temporal, parietal and prefrontal regions has been associated with WM accuracy in healthy controls (Haenschel, et al., 2007) and patients with schizophrenia (Quintana, et al., 2003; Schlosser, et al., 2008; Walter, et al., 2007; R. C. Wolf, et al., 2007) interventions that enhance activity in these regions could be particularly effective to improve cognitive functions in patients with schizophrenia. Wolf et al. have shown that improvement of WM accuracy in patients after multi-modal treatment to a level seen in controls correlated with decreased thought disorder and cognitive deficits (R. C. Wolf, et al., 2007). Furthermore, enhancement of frontal function during WM as well as performance improvement in other cognitive functions has been reported after pharmacological treatment

with both typical and atypical anti-psychotics (Green, et al., 1997; Honey, et al., 1999; Sharma & Mockler, 1998). Hyperactivation of the left LPFC has been reported during WM in patients treated with an atypical anti-psychotic compared to controls, which was also correlated with amelioration of WM performance (Meisenzahl, et al., 2006). Furthermore, improvement of WM performance associated with enhanced frontal activation in patients with schizophrenia has been reported after pharmacological treatment with flumazenil an inhibitor of GABAergic neurotransmission (Menzies, et al., 2007).

However the beneficial effects of typical and atypical anti-psychotics on cognitive functioning appear to be small, vary between cognitive domains, and are influenced by practice effects (T. E. Goldberg, et al., 2007; Keefe, et al., 2007). Besides such a neurotransmitter system-based treatment of cognitive deficits the modification of other targets such as neuronal activity-regulated proteins and RNAs involved in neuroplasticity may be more effective. In particular as these new targets would not only respond to neuropharmacological agents but also to interventions at the neural network (e.g. neurofeedback) and behavioural level. Our findings of enhanced activity associated with accurate WM performance in highly functional patients with schizophrenia together with cognitive remediation studies in schizophrenia (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007) suggest that neurofunctional adaptations can compensate for pathophysiological changes in schizophrenia.

Conclusion

The results of our study combined with previous findings support a model where hypofrontality in high-functioning patients is explained by compensation through hyperactivity in contralateral homologue areas and sensory areas. Our study also suggests the enhancement of working memory-related brain activity as a new target for clinical interventions.

Acknowledgements

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Chapter III - a theoretical article

Biological pathways to adaptability –interactions between genes and environment for adaptive behaviour.

I am currently revising this article for Genes Brain and Behaviour with the title and authors as indicated below.

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Abstract

Because living systems depend on their environment (e.g., energy consumption, space), the evolution of environmental adaptability is inseparable from the evolution of life itself (Pross, 2003). In animals and humans, environmental adaptability extents further to adaptive behaviour. More recently it has emerged that individual adaptability depends on the interaction of adaptation mechanisms at diverse functional levels. This interaction enables the integration of genetic, epigenetic and environmental factors for the coordinated regulation of adaptations at these different functional levels. First, we present the basis for the regulation of adaptation mechanisms across functional levels. Then, we focus on neuronal activity-regulated adaptation mechanisms that involve the regulation of gene expression to change the structural and functional properties of neurons. Finally, we discuss a number of key regulatory proteins and microRNAs and their consequences on brain structure, function and behaviour. Most of the evidence so far is based on invasive sampling of animal tissue or post-mortem studies in humans. However, we also present techniques that combine genetic with behavioural and neurophysiological measures in humans (for example genetic imaging) and discuss their potential and limitations. We propose that the influence of variations in DNA sequences that code for proteins or RNA involved in the regulation of gene expression needs to be considered if we want to understand the biological underpinnings of individual variations in behaviour and cognitive performance.

On the origin of adaptability

The evolution of adaptability was central for the evolution of life (Pross, 2003) because living systems depend on their environment, e.g. for the continuous consumption of energy.

Adaptability requires self-variation. Imperfect self-replication[6] has been proposed as being at the origin of diversification and selection of systems with teleonomic[7] properties (Lifson, 1987). Errors during self-replication can produce exponential diversity as long as the net replication is positive[8] (Lifson, 1987, 1997). Diversity enables environment-dependent selection and thereby adaptation to the environment. Imperfect self-replication is thus a mechanism that combines self-replication with self-variation. Incorporation of a dissipative reaction[9] is necessary because imperfect self-replication is a thermodynamically unfavourable reaction (Pross, 2003). The dissipative reaction depends on an energy source in the environment.

Increasing structural and functional complexity[10] enhances the capability to replicate through a variety of catalytic effects and increases the energy demand (Pross, 2003). Increasing complexity not only increases the number of changes but also the variety of mechanisms to induce such changes. The positive selection of changes that improve the energy gathering reaction thus enable the further increase of complexity, replication capability (or reproduction ability) as well as the variability during imperfect self-replication. This circularity implies the coevolution of imperfect self-replication, energy gathering reaction and structural/functional complexity. For these reasons imperfect self-replication is a diversification mechanism for natural selection that can explain the importance of the dynamic interaction between living

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[6]Self-replication – autocatalytic process whereby the self-replicating element (A) accelerates its own reproduction, this reaction exhibits enormous kinetic power (exponential growth) → number of A= $\exp(n \cdot \ln 2)$, if the self-replication is imperfect the newly produced self-replicating element is a modified copy → mechanism for self-variation, the energy and material to produce more of the self-replicating element is supplied by reactants (R) that leave the reaction as thermodynamically more stable waste (W) → dissipative reaction (towards the state of equilibrium), thus the replication reaction (away from the thermodynamic equilibrium) becomes possible:
$2^{n-1} \cdot R + 2^{n-1} \cdot A \rightarrow 2^{n} \cdot A + 2^{n-1} \cdot W$

[7] The teleonomic character of life manifests in is purposeful organization and behaviour, e.g. the replicating molecule has a structure that enables replication (Lifson, 1987; Pross, 2003).

[8] Positive rate of net replication means that the number of replicating elements that are produced exceeds the number of those that are decomposed.

[9] The free energy that is released during the dissipative reaction when reactants change from a higher to lower energy state can be used for the replication reaction. Such reactions towards the equilibrium are thermodynamically preferred. The availability of reactants for the dissipative reaction from the environment limits the self-replication.

[10] Complexity depends on the number and individual functions of all units and their interactions. Biological complexity – structural, organizational and informational complexity, e.g. genes that control each other and form networks → emergence of new properties

systems and their environment in the evolution of complexity and metabolism (Lifson, 1987, 1997; Pross, 2003).

The evolution of multi-cellular complexity has been supported by the superior energy yield of aerobic metabolism[11] that evolved with the development of an oxygenic environment (Koch & Britton, 2008). Supported by improved energy supply, more complex organisms with diverse, functional levels (molecular, cellular, systemic and behavioural) evolved, capable of intra[12]-and trans[13]-generational adaptability via multiple self-variation mechanisms[14] at each functional level. The coordinated regulation of adaptations at these different functional levels depends on the interactions between self-variation mechanisms to integrate genetic, epigenetic and environmental factors. Some of these adaptive changes are heritable. How these self-variation (adaptation) mechanisms interact to regulate adaptations and thus control the adaptability of an individual during its own lifetime and also across generations is a core question of contemporary research.

The nervous system - a self-variation system for the interaction with the environment

The complexity of the nervous system (NS) correlates with the environmental complexity and diversity to which a species is adapted (Emes, et al., 2008; Shumway, 2008; Silk, 2007). The NS enables the temporal and spatial regulation of adaptations for the interaction between individual and environment. It mediates, coordinates and represents via peripheral and central nervous systems, the interaction with the individual's external environment and its internal environment (all other systems of an organism). By coupling adaptation mechanisms at the organism's molecular, cellular, neural network and behavioural levels the NS integrates

[11] The complete oxidation of glucose to CO_2 and H_2O yields ca 30 ATP compared to ca 3 ATP gained from anaerobic glycolysis.

[12] Intra-generational adaptability is the ability of one individual to adapt (e.g., mutation, regulation of gene expression, structure, function, behaviour).

[13] Trans-generational adaptability can be inherited by genetic, epigenetic mechanisms and learning.

[14] Self-variation mechanisms range from imperfect self-replication (e.g. mutations, copy errors in DNA) to regulative processes like changes of the epigenome, protein expression, morphology, physiology and behaviour.

environmental and internal signals. The regulation and variation mechanisms at those different functional levels as well as their interactions increase the adaptability of an individual. Gaining insight into these adaptation mechanisms and their interaction at the involved functional levels will help to unravel how interactions between genes and environment shape individual behaviour.

Genetic and epigenetic adaptability

Variation at the genome level includes changes of the genome and its epigenome[15]. Genome and epigenome dispose of intra-generational adaptability and if they are inherited also trans-generational adaptability. While changes of the genome and epigenome can occur in every DNA containing cell, only dividing cells can inherit those changes. In complex multi-cellular organisms somatic cells that divide can transfer genetic and epigenetic changes within cell-lineages and germ cells transfer genetic and epigenetic changes across generations of individuals.

Variation of the genome or epigenome can only affect phenotypic variation if they modify the genome's output by changing the transcriptome[16] and/or translatome[17]. Such changes can be initiated by variation of the genome via change of DNA sequence (including single nucleotide variation (SNPs), structural variation (ranging from a few base pairs to whole genome sequence rearrangement, deletion, insertion and repetition) and DNA recoding by DNA repair/editing enzymes) and/or DNA configuration (chromatin remodelling[18], DNA-

[15] Epigenome refers to anything exclusive of DNA sequence that would be inherited during meiosis and/or only mitosis. Such heritable things include molecules (e.g. RNAs, proteins) and sub-cellular structures (e.g. mitochondria) as well as the dynamic configuration of DNA (the configuration of nucleotides, histones, non-histone-chromatin proteins and chromatin). Therefore cells with the same genome sequence can have different epigenomes. Epigenetic changes initiated by endogenous or environmental factors are important for the regulation of gene expression, e.g. via DNA-methylation/demethylation.

[16] Transcriptome is the total of DNA transcribed into RNAs.

[17] Translatome is the total of mRNAs translated into amino acid sequences.

[18] Chromatin remodelling refers to changes in the interaction between DNA and histones by chromatin remodelling proteins e.g. by histone modification enzymes and multi-protein chromatin remodelling complexes.

methylation) and/or genome output regulators (non-coding RNAs[19], transcription factors, hormones, enzymes, etc.). Naturally all these different modes of change can interact with each other, as in the case of mutations in genes encoding regulators for epigenetic regulation (Ooi & Wood, 2008). Factors that regulate the genome's output through these variation mechanisms could influence the timing and location of genetic and epigenetic changes to allow phenotypic adaptation in response to the specific selective pressure (Rando & Verstrepen, 2007). The non-random distribution of changes in the genome suggests selection differences between regions (Venter, et al., 2001), which may result from differences in selective pressures between phenotypes (Rando & Verstrepen, 2007). Thus phenotypes under high selective pressure are more variable. Recent observations point to a correlation between genetic variation mechanisms, phenotypic variability and the variability of the acting selective pressures (Rando & Verstrepen, 2007). For example a genetic change responsible for the adaptation of camouflage in mice coincided with the colour change of the mice's habitat (Linnen, Kingsley, Jensen, & Hoekstra, 2009). Certain mutations show a higher frequency under positive selection as long as the selective pressure is non-lethal (Shapiro, 1995). The spectrum of DNA sequence changes differs during unselected und selected exponential growth in bacteria (Rosenberg, Longerich, Gee, & Harris, 1994). Homologous recombination and plasmid gene transfer have been shown to induce genetic changes to adapt metabolic functions in response to the change of metabolic substrates in bacteria (Foster & Trimarchi, 1995; Radicella, Park, & Fox, 1995). Hence cells are equipped with biochemical systems to change their DNA in response to selective pressures on phenotypes like metabolism (Shapiro, 1995).

A significant part (> 40%) of human DNA (Lander, et al., 2001) consists of small, repetitive, mobile DNA control elements (transposons) discovered by Barbara McClintock (McClintock, 1951). Most of these transposons refer to the type retrotransposons (Lander, et al., 2001) that

[19] Non-coding RNA is RNA transcribed from DNA that does not encode amino acid sequences and instead serves as diverse types of RNA a variety of functions.

transcribe DNA-driven RNA into DNA (reverse transcriptase) before this DNA copy "jumps" into a new position in the genome (Ostertag & Kazazian, 2001). Retrotransposition thus represents a mechanism to vary the copy number of DNA sequences. Only about 65 of such retrotransponsons that belong to the LINE-1 (long interspersed nuclear elements) family are estimated to still be functional in any human genome today and transpositions occur at very low frequencies (Ostertag & Kazazian, 2001). The remaining transposons (including retro- and DNA transposons) are considered to be fossils that have lost their functionality in the course of evolution (Ostertag & Kazazian, 2001). If activated LINE-1 elements catalyse modifications ranging from small DNA sequence changes to large genomic rearrangements, that can alter gene regulation and thus could contribute to phenotypic diversity including individual variability in susceptibility to complex diseases (Muotri, et al., 2005; Muotri, Marchetto, Coufal, & Gage, 2007; Muotri, Zhao, Marchetto, & Gage, 2009; Ostertag & Kazazian, 2005, 2001).

In bacteria the frequency of transpositions is regulated in response to environmental signals suggesting some adaptive function (Hall, 1999). Because the mobility of these elements is regulated by ncRNAs (e.g., miRNAs) and proteins in response to different types of cellular stress, e.g. virus infections (van Rij & Berezikov, 2009) through their effects on gene expression they may contribute to individual adaptability.

Accordingly, genetic variation mechanisms, which are encoded in the complex architecture of the genome, themselves appear to be under selection during evolution. The selection of these genetic variation mechanisms would depend on their capacity to generate phenotypic variability (e.g. through adaptive mutation) that can "cope" with the selective pressure acting on the specific phenotype. This suggests that variability could be generated via diverse variation mechanisms if, where and when it is most likely to improve adaptability.

The impact ("use") of these diverse variation mechanisms is presumably regulated by each cell individually and also depends on the cell's environment. This would allow cell-specific changes of genomes in response to cell-specific environmental pressures.

Another mechanism that has been suggested to generate environmentally-driven DNA/RNA sequence variability in protein-coding and ncRNA-coding sequences of immune and nervous system cells is the editing or recoding of DNA or RNA (J. S. Mattick & Mehler, 2008). DNA recoding could be the reason for DNA sequence variations in antibody receptor genes that are generated to provide the receptor diversity of antibodies required to recognize new antigens (J. S. Mattick & Mehler, 2008). Genes encoding DNA/RNA editing enzymes show signs of strong positive selection in the human genome (J. S. Mattick & Mehler, 2008). RNA editing is most active in the brain, important to brain function and humans show 2-fold increase of editing compared to mice (J. S. Mattick & Mehler, 2008). Most of this editing occurs in primate-specific non-coding RNA sequences e.g., in the UTRs of mRNA, and this mechanism has been related to the increased cognitive capacity of primates (J. S. Mattick & Mehler, 2008). Thus RNA editing could be an important molecular mechanism for the regulation of neural development and plasticity, e.g. by modifying sequences and biophysical properties of glutamate and serotonin receptor subunits to modulate synaptic strength and neural network connectivity (J. S. Mattick & Mehler, 2008). It has also has been speculated that coupling of RNA to DNA editing and its coordination among synapses, neurons and neural networks would allow the genetic encoding of environmentally-driven changes in neural structure and function during brain development and cognitive plasticity (J. S. Mattick & Mehler, 2008). One could extend this speculation to the question how adaptation mechanisms in neurons, immune cells and germ cells could be coordinated to increase the intra-and transgenerational adaptability of an individual.

In summary genetic and epigenetic adaptation mechanisms are extraordinary versatile and are regulated in response to internally and environmentally-driven signals. Although the evidence

is still spare it seems likely that the selection of genetic and epigenetic variation mechanisms depends on their capacity to generate phenotypic adaptations in response to selective pressures. If genetic changes like mutations can be regulated i.e., induced or suppressed in response to the presence or absence of such pressures they belong into the "toolbox" of complex individual adaptability and not to chance.

Interaction of adaptation mechanisms across functional levels

Sensory input or behaviour that modulates the activity of specific neural networks can drive activity-dependent changes at the molecular, synaptic and cellular level. Conversely, these activity-dependent adaptations can temporally and spatially modulate the activity within networks and thus adapt cognitive capacity and sensory acuity (Kempermann, Kuhn, & Gage, 1997; Paylor, Morrison, Rudy, Waltrip, & Wehner, 1992; Prusky, West, & Douglas, 2000). The regulation of neuronal properties is part of the regulation of neural network properties. Regulation of network properties enables the reorganisation of neural networks. Such reorganisation processes are presumably required for the updating of past with new experiences, increasing processing efficiency and capacity for learning and memory (Dudai, 2004; Miyashita, Kubik, Lewandowski, & Guzowski, 2008; Shema, Sacktor, & Dudai, 2007). The ongoing adaptation process within individual neurons as well as neural networks depends on the dynamic intergation of internal and environmental changes (signals). For example reorganization of neural networks during learning depends on activity-induced remodelling of synaptic properties between neurons requiring neuronal adaptations that depend on molecular changes (signals). How these adaptations are coordinated at the molecular, cellular and network level to enable learning and memory processes is far from being understood.

The regulation of transcriptome, translatome and proteome[20] are mechanisms of molecular adaptation that contribute significantly to neuroplasticity[21]. Collectively the various cell types

[20] Proteome is the total of proteins expressed.

of the NS express 80% of the coding genome, exceeding gene expression of any other organ (Ooi & Wood, 2008). The transcription-dependent neuroplasticity during learning and memory involves chromatin remodelling (Levenson, et al., 2004; Levenson & Sweatt, 2005; Vecsey, et al., 2007) and DNA-methylation (Miller & Sweatt, 2007). Adaptation mechanisms involved in learning and memory like synaptic strength (Barco, Alarcon, & Kandel, 2002; Plath, et al., 2006) and dendritic growth (Wayman, et al., 2006; Zhou, et al., 2006) have been shown to depend on the coordinated expression of multiple genes in response to neural activity. Fonseca et al. have suggested that the strength of neuronal activity determines the dependency of long-term potentiation (LTP) [22] on protein synthesis (Fonseca, Nägerl, & Bonhoeffer, 2006). The neuronal activity-dependent regulation of transcription and translation allows for the dynamic and local adaptation of quantity and type of neuronal proteins and other functional molecules. Rapidly induced post-translational modification and trafficking of pre-existing proteins appear to be important for regulation and maintenance of protein functions. Neuronal adaptation by regulation of pre-existing mRNA is limited to the type and quantity of available mRNAs. The neuroplasticity that includes DNA expression requires more time, energy and regulation but increases adaptability compared with neuroplasticity restricted to post-transcriptional or post-translational regulation. The regulation of these neuronal plasticity mechanisms is coordinated by intracellular signalling systems and depends on neuronal activity and other extracellular signals. Intracellular signalling systems can amplify signals to operate as a biochemical switch from low to maximal activation, realize time and location-dependent integration of diverse extracellular signals, induce transient or long-lasting activation of effector molecules and respond to positive or negative feedback mechanisms (Adams & Sweatt, 2002). Hence, intracellular

[21] Neuroplasticity is the adaptability of neurons in response to stimuli for which they are receptive. Neuronal adaptations range from instant to long-lasting and from molecular to morphological changes.
[22] LTP is a long-lasting potentiation of synaptic transmission.

signalling systems can coordinate the type and duration of adaptations at the molecular, synaptic and neuronal level with high input-specificity.

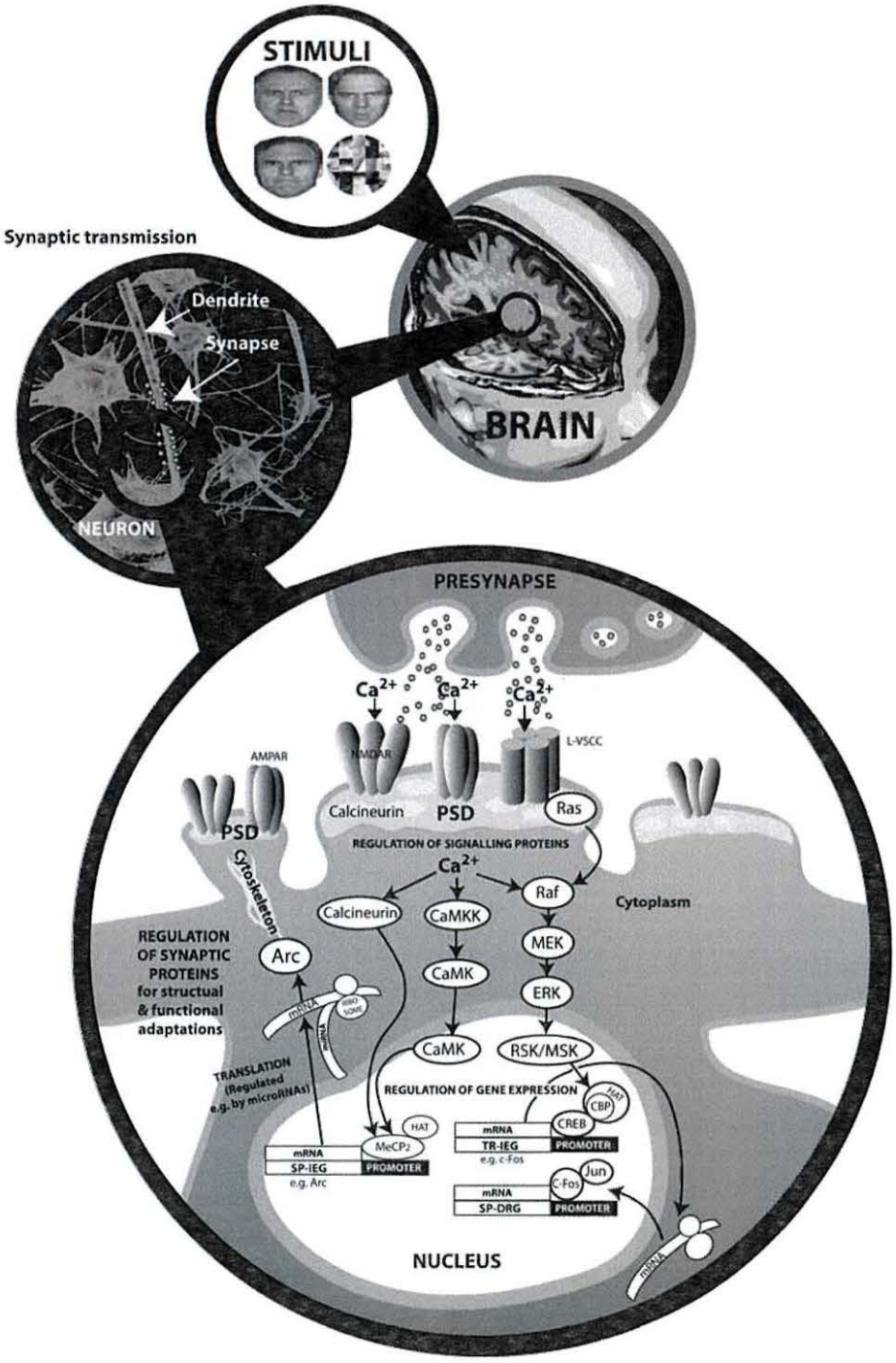

Fig.1 Stimuli activate neural networks involving synaptic transmission between neurons.

Extracellular stimuli activate intra-neuronal signalling proteins, which is mediated by Ca^{2+}. Depending on the Ca^{2+}-signal signalling proteins regulate and coordinate the adaptation of neuronal properties by changing pre-existing proteins, mRNA translation and gene expression. Changes of gene expression require the regulation of transcription factors inside the nucleus. These neuronal activity-regulated transcription factors regulate immediate early genes (IEGs) that can encode other transcription factors (TR) or synaptic proteins (SP). MicroRNAs can regulate the transport and translation of mRNA for

transcription factors or synaptic proteins. De novo synthesis of IEG transcription factors is required to regulate the gene expression of delayed response genes (DRGs) that encode synaptic proteins. These molecular adaptation mechanisms lead to structural and functional changes of neurons, thus providing the basis for neuroplasticity and short-or long-lasting functional adaptations of neuronal properties. The adaptation of neuronal properties allows the functional adaptation of neural networks to regulate adaptations of the behavioural response, e.g. the memorizing of certain stimuli.

Functional and structural adaptation of neurons

Developmental and activity-dependent adaptation of neuronal structure and function depends on the processing of extracellular signals (conveyed mainly by neurotransmitters, neuromodulators, neurotrophines, hormones, and cytokines, etc.) that regulate the adaptation of the neuronal protein network via intracellular signalling systems (**Fig.1**). The coordination of specific signalling pathways mediates input-specific modifications. Intracellular signalling can have local effects on the function of pre-existing synaptic molecules (e.g. mRNA, proteins) or, if converted into an intra-nuclear signal, on gene expression. The conversion of an extracellular signal (first messenger) into an intracellular signal (second messenger) depends on the signal and receptor properties. Receptors coupled to intracellular second messenger systems can regulate the activity of enzymes (e.g., protein kinases/ phosphatases, phospholipases), which regulate target proteins (e.g., structural proteins, signalling enzymes, ion channels/pumps and transcription factors/cofactors). For example the Ca^{2+}-second messenger system involves Ca^{2+}-binding proteins (e.g., phospholipase C and A_2, protein kinase A/C, calmodulin, calcineurin). These proteins can regulate Ca^{2+}-dependent signalling enzymes, e.g. Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) that can recruit transcription factors and cofactors to the promoters of neuronal activity-dependent genes (West, et al., 2001). Transcription factors that regulate activity-dependent gene expression, like cAMP response element binding protein (CREB), myocyte enhancer factor 2 (MEF2), nuclear factor of activated T cells (NFAT), methyl-CpG-binding protein 2 (MeCP2) and serum response factor (SRF), can be a part of the transcription machinery and/or involved in chromatin remodelling (S. Cohen & Greenberg, 2008; West, et al., 2001). Transcription factors can change the activity-dependent expression of their target genes within minutes.

Such target genes include those coding for activity-induced transcription factors, like *c-Fos* and *nerve growth factor-inducible protein A* (*NGFI-A*) and for a large range of cellular function proteins, e.g. activity-regulated cytoskeleton-associated protein (*Arc*), *Homer 1a* and brain-derived neurotrophic factor (*BDNF*) (Miyashita, et al., 2008). Expression of these immediate-early genes (IEGs) is independent of *de novo* protein synthesis or transcription of other genes (Miyashita, et al., 2008). Activity-induced IEGs that encode transcription factors in turn regulate the transcription of delayed response genes (DRGs) (Miyashita, et al., 2008). The transcription of DRGs therefore depends on these *de novo* synthesized transcription factors. DRGs encode proteins for long-term changes in neuronal functions, e.g. neurotransmitter and hormone receptor genes. Activity-regulated genes are expressed with distinct kinetics, differences in stimulus-responsiveness, cell-type and region-specificity (Flavell & Greenberg, 2008; Miyashita, et al., 2008) and this activity-dependent regulation of gene expression patterns in neural networks has been found to distinguish stages of learning and memory (Miyashita, et al., 2008). Furthermore the combined expression of learning state independent and learning state dependent IEGs (Miyashita, et al., 2008) may increase the range and thus the input-specificity of synaptic modifications. Neuronal activity-regulated proteins play central roles in the adaptation of metabolism, cytoskeleton changes, signalling pathways, neurotransmitter exocytosis, neuronal morphology and survival, number and properties of synapses and receptors. These molecular, synaptic and cellular adaptations can modify the properties of neuronal networks to facilitate behavioural adaptability.

In addition to regulatory proteins, various types of non-coding RNAs (ncRNAs) regulate genes and proteins involved in neuroplasticity (Mehler & Mattick, 2006). These ncRNAs contain regulatory sequences instead of protein-coding sequences and are transcribed from DNA together with protein-coding sequences, e.g. as untranslated regions (UTRs) and introns or independently of protein-coding sequence, e.g. from intergenic regions or antisense strands.

Regulatory ncRNAs dispose of cis-and/or trans-acting[23] elements to engage in RNA-RNA, RNA-DNA, and RNA-protein interactions (J. Mattick & Gagen, 2001). In this way they can regulate chromatin remodelling, transcription, mRNA processing, translation, mRNA stability and subcellular location, protein stability, activity and secretion (Costa, 2007; J. Mattick & Makunin, 2006; Szymański, Barciszewska, Zywicki, & Barciszewski, 2003). Among the numerous regulatory ncRNAs expressed in the brain recent investigations have started to unveil the functions of neuronal microRNAs (miRNAs) (Klein, Impey, & Goodman, 2005). By binding with varying sequence compatibility to cis-acting elements in 3'UTR, miRNAs can regulate the transport and translatability of mRNA targets in developing and mature neurons (Kosik, 2006). The translational repression of synaptic proteins by miRNAs has been shown to regulate dendritic growth (Klein, et al., 2007; Schratt, et al., 2006; Wayman, Davare, et al., 2008). Moreover, the transcription of IEG miRNA can be enhanced by neuronal activity (Wayman, Davare, et al., 2008).

Neuronal activity-regulated proteins and microRNAs involved in neuroplasticity

This overview provides examples of how proteins and RNAs (**Tab.1a-b**) that can be regulated by neuronal activity can regulate the neuron's structural and functional properties and how this regulation can influence behaviours and pathology.

[23] The cis-acting element is the target sequence of the regulated molecule to which the regulator binds with its trans-acting element (sequence).

Table 2a – Activity-regulated proteins and miRNAs

Regulator (subcellular functions and locations can differ between protein isoforms)	**Expression in the brain** (can differ between protein isoforms)	**Neuronal adaptations, affected behaviours, neuropathologies**
Arc – activity-regulated IEG encoding synaptic cytoskeleton protein regulates synaptic proteins	hippocampus, amygdala, insula, entorhinal cortex, anterior cingulate cortex, DLPFC, orbital frontal cortex, ventral tegmental area, substantia nigra, striatum, caudate, putamen, nucleus accumbens, sensory and motor cortices	- structural, functional, neuronal survival - memory, learning - stress disorders (Kozlovsky, et al., 2008; Molteni, et al., 2009; Ons, Marti, & Armario, 2004), depression (de Foubert, O'Neill, & Zetterstrom, 2007), addiction (Bramham, et al., 2009; Pandey, et al., 2008), cognitive impairment (D. C. Wang, Chen, Lee, & Chen, 2006)
CREB – activity-regulated transcription factor cAMP response element binding protein regulates IEGs for transcription factors and synaptic proteins	hippocampus, amygdala, entorhinal cortex, PFC, occipital cortex, nucleus accumbens, ventral tegmental area, striatum	- structural, functional, promotes neuronal survival - memory, learning, emotion, stress response - major depression (Boer, et al., 2007; Hettema, et al., 2009; Perlis, et al., 2007), addiction (McClung & Nestler, 2003; Moron, et al., 2009), anxiety (D. L. Wallace, et al., 2009), cognitive impairment (Bourtchuladze, et al., 1994), sexual behaviour (Barrot, et al., 2005), schizophrenia (Kawanishi, Harada, Tachikawa, Okubo, & Shiraishi, 1999), AD[24] (Smith, Pozueta, Gong, Arancio, & Shelanski, 2009), Rubinstein-Taybi syndrome (Alarcon, et al., 2004), Huntington's disease (Okamoto, et al., 2009)
CaMKs – Ca^{2+}/calmodulin-dependent kinases, activity-regulated signalling protein isoforms, regulate multiple proteins in synapse, cytoplasm and nucleus	DLPFC, hippocampal formation, caudate, putamen, thalamus, hypothalamus, midbrain and visual cortex	- structural, functional, promotes neuronal survival - memory, learning - AD (Gandy, Czernik, & Greengard, 1988; Z. Gu, Liu, & Yan, 2009), addiction (Kim, Ahn, Go, Wang, & Choe, 2009; Licata & Pierce, 2003; Marin, et al., 2009; Pierce & Kalivas, 1997)
Calcineurin – activity-regulated phosphatase, regulator of multiple proteins in synapse, cytoplasm and nucleus	hippocampus, thalamus, striatum, nucleus accumbens, somatosensory cortex, PFC, cerebellum	- functional, structural - learning, memory - schizophrenia (Eastwood, Burnet, & Harrison, 2005; Gerber, et al., 2003; Yamada, et al., 2007), AD (Abdul, et al., 2009; Kuchibhotla, et al., 2008; Q. Lian, C. J. Ladner, D. Magnuson, & J. M. Lee, 2001; Taglialatela, Hogan, Zhang, & Dineley, 2009)
c-Fos – activity-regulated IEG encoding transcription factor, regulates the transcription of DRGs	PFC, anterior cingulate, sensory and motor cortices, caudate, putamen, nucleus accumbens, striatum, paraventricular nucleus, hypothalamus, medulla, amygdala, hippocampus	- structural, functional, promotes neuronal survival - attention, emotion, memory, learning, stress-response, sleep regulation - addiction (Caster & Kuhn, 2009; M. Xu, 2008), anxiety (Kabbaj & Akil, 2001; A. M. Linden, Greene, Bergeron, & Schoepp, 2004; Salomons, et al., 2009)
Homer1 – activity regulated IEG and continuously expressed gene encoding scaffolding protein isoforms that regulate synaptic proteins	PFC, striatum, nucleus accumbens, ventral tegmental area, thalamus, parietal cortex, occipital cortex, amygdala and hippocampus	- structural, functional - attention, memory, emotion, stress response - schizophrenia (Norton, et al., 2003; K. Szumlinski, Kalivas, & Worley, 2006), addiction (Swanson, Baker, Carson, Worley, & Kalivas, 2001; K. K. Szumlinski, et al., 2006; K. K. Szumlinski, et al., 2004; Yano & Steiner, 2005; G. C. Zhang, et al., 2007), anxiety (Klugmann, et al., 2005)

[24] Alzheimer's Disease

Table 1b – **Activity-regulated proteins and miRNAs**

Regulator (subcellular functions and locations can differ between protein isoforms)	**Expression in the brain** (can differ between protein isoforms)	**Neuronal adaptations, affected behaviours, neuropathologies**
Mitogen – activated/extracellular-regulated protein kinase (**MAPK/ERK**) isoforms are signalling proteins that regulate proteins in synapse and nucleus	hippocampus, amygdala, basal ganglia, thalamus, hypothalamus, striatum, substantia nigra, cerebellum, visual cortex, PFC	- functional and structural - learning, memory - addiction (Ferguson, Fasano, Yang, Brambilla, & Robinson, 2006; L. Lu, et al., 2005; L. Lu, Koya, Zhai, Hope, & Shaham, 2006; Sanna, Simpson, Lutjens, & Koob, 2002; J. Q. Wang, Fibuch, & Mao, 2007), AD (Dineley, et al., 2001; Giovannini, et al., 2008; Greenberg, Koo, Selkoe, Qiu, & Kosik, 1994; Savage, Lin, Ciallella, Flood, & Scott, 2002; Zhu, et al., 2003)
MeCP2 – Methyl-CpG Binding Protein 2, activity-regulated transcription factor, regulates IEGs for transcription factors and synaptic proteins	hippocampus, amygdala, visual cortex, hypothalamus, frontal cortex, caudate, putamen	- functional and structural - learning, memory - Rett and Rett-like syndromes (Abuhatzira, Shemer, & Razin, 2009; Chahrour & Zoghbi, 2007; Monteggia & Kavalali, 2009; Samaco, et al., 2009), autism (Coutinho, et al., 2007; Loat, et al., 2008; Nagarajan, Hogart, Gwye, Martin, & LaSalle, 2006; Zoghbi, 2003)
MEF2 – Myocyte Enhancing Factor, activity-regulated transcription factor, regulates IEGs for transcription factors and synaptic proteins	hippocampus, cerebellum, thalamus, frontal cortex, nucleus accumbens, striatum, visual cortex	- functional, structural, regulates neuronal differentiation, migration and survival - locomotor sensitization - addiction (Pulipparacharuvil, et al., 2008), Rett syndrome (H. Li, et al., 2008), autism (Morrow, et al., 2008), AD (Burton, Dibrov, Kashour, & Amara, 2002; Gonzalez, et al., 2007; X. Wang, She, & Mao, 2009)
NFAT- Calcineurin/BDNF/PKC-activated Nuclear factor of Activated T-cells, activity-regulated transcription factor, regulates pro-survival DRGs	hippocampus (all 4 isoforms), amygdala, frontal cortex, cerebellum, substantia nigra, basal ganglia, thalamus, hypothalamus	- functional, structural and regulates neuronal survival - memory - addiction (R. D. Groth, et al., 2008)
NGFI-A - Nerve Growth Factor-Inducible protein A = Zif268/Erg-1/Krox-24/TIS8/ZENK, activity-regulated IEG and continuously expressed gene encoding transcription factor, regulates expression of DRGs	hippocampus, amygdala, basal ganglia, thalamus, hypothalamus, visual cortex, somatosensory cortex, cingulate, brainstem, cerebellum, raphe nucleus, and auditory cortices	- functional and structural and may neuronal survival - short and long-term memory, sensory information processing, arousal, motivation, emotion, stress responses, exploratory behaviour - maternal depression affects NGFI-A-regulated glucocorticoid receptor expression and stress-response (cortisol level) in neonates (Oberlander, et al., 2008)
miR-134- expression temporally and spatially regulated by extra-cellular signals, regulates translation of synaptic proteins	primary cortex, cerebellum, hippocampus	- structural - AD (Hebert & De Strooper, 2009)
miR-132-expression regulated by neuronal activity, regulates translation of synaptic proteins	hippocampus	- functional and structural - AD (Hebert & De Strooper, 2009; Lukiw, 2007)

Activity-regulated synaptic cytoskeleton protein

Neuronal-activity dependent transient transcription and translation of the IEG *Arc* has been reported for many brain regions such as hippocampus, amygdala, neocortex and striatum (Miyashita, et al., 2008). NMDA receptor-mediated LTP can initiate the transient expression of *Arc* within 1-2min (Guzowski, McNaughton, Barnes, & Worley, 1999). Newly synthesized, *Arc* mRNA is trans-located to activated excitatory post-synapses (Steward, Wallace, Lyford, & Worley, 1998; Steward & Worley, 2001) for consecutive protein synthesis (Moga, et al., 2004). Arc protein situated in the postsynaptic density (PSD) of glutamatergic neurons interacts with signalling, cytoskeleton and endocytosis proteins (Miyashita, et al., 2008) thereby regulating dendritic growth and AMPA receptor numbers (Chowdhury, et al., 2006; Rial Verde, Lee-Osbourne, Worley, Malinow, & Cline, 2006; Shepherd, et al., 2006). It has been associated with hippocampal late LTP and LTD–dependent memory formation (Plath, et al., 2006).

cAMP response element binding protein

The transcription factor CREB activates Ca^{2+} and cAMP-dependent transcription (Sheng, McFadden, & Greenberg, 1990). This involves coactivators e.g., CREB-binding protein (CBP) with intrinsic histone acetyltransferase activity (HAT) to remodel chromatin, and the recruitment and stabilization of RNA polymerase II (Flavell & Greenberg, 2008). Essential for its role in activity-dependent gene expression, the activity of CREB is regulated by various protein kinases and phosphatases (Greer & Greenberg, 2008). CREB has been proposed as a major contributor to the molecular transition from short- to long-term synaptic plasticity by facilitating hippocampal late-LTP (Barco, et al., 2002). Target genes regulated by CREB and CaMK activity include *c-Fos*, *BDNF*, *CPG15/neuritin, wnt-2* and *miR-132*, which likely mediate activity-dependent dendritic outgrowth (Flavell & Greenberg, 2008; Korte, 2008; Tanaka, et al., 2008). CREB has also been implicated in the stress response as

one of the regulators of *corticotropin-releasing hormone* gene (CRH) transcription (Y Liu, Kamitakahara, Kim, & Aguilera, 2008). The responsiveness of neurons in the nucleus accumbens is also modulated by CREB (Dong, et al., 2006). Genetic variability in *CREB1* has been linked to anger expression in patients with major depression, particularly in males (Perlis, et al., 2007). Further changes in CREB activity or expression have been implicated in emotional reactions, reward/aversion (Barrot, et al., 2002; Barrot, et al., 2005; Carlezon, Duman, & Nestler, 2005) and suicide risk (Dwivedi, et al., 2003).

CaMKs

Ca^{2+}/calmodulin-dependent kinases are Serine/Threonine protein kinases that phosphorylate Ser/Thr residues of their protein substrates (Wayman, Lee, Tokumitsu, Silva, & Soderling, 2008). The co-localisation of CaMKs with their substrates within multiprotein signalling complexes like PSD or subcellular compartments like the nucleus or membranes determines their signalling specificity and activation kinetics (Wayman, Lee, et al., 2008). Various CaMK-isoforms contribute to the temporal and spatial regulation of neuronal activity-dependent transcription and translation. The modulation of α-CaMKII activity by NMDA receptor NR2B subunit can modify AMPA receptor function involved in LTP (Wayman, Lee, et al., 2008). Mutation-induced interference with α-CaMKII function impairs NMDAR-dependent LTP in a region-specific manner (Lamsa, Irvine, Giese, & Kullmann, 2007). Brain structure and function in healthy individuals have both been shown to be influenced by genetic variation in α-CaMKII (Rasetti, et al., 2007). CaMKK and CaMKI regulate axonal elongation or activity-dependent dendritic growth (Wayman, Lee, et al., 2008).

Calcineurin/protein phosphatase 2B

Activity-regulated Ca^{2+}/calmodulin-dependent Ser/Ther phosphatase calcineurin/ protein phosphatase 2B contributes to short- as well as long-term neuronal adaptations (R. Groth,

Dunbar, & Mermelstein, 2003). Genetic disruption of calcineurin impaired hippocampus-dependent working memory and episodic-like memory but not reference memory through changes in LTD and LTP (Zeng, et al., 2001). Furthermore these knockout mice showed multiple abnormal behavioural traits that have been likened to symptoms of schizophrenia, including increased locomotor activity, decreased social interaction, and impaired attention (Miyakawa, et al., 2003). Calcineurin is enriched in PSDs and the cell soma and can be targeted to its regulators and substrates in subcellular compartments and cytoplasm (R. Groth, et al., 2003). Calcineurin is involved in the regulation of synaptic vesicles, endocytosis of AMPA receptors, NMDA and $GABA_A$ receptor activity, LTD-mediation by presynaptic group II metabotropic glutamate receptors and the synthesis of NO and GABA (R. Groth, et al., 2003). The inhibitors of protein phosphatase 1 (PP1) are deactivated by calcineurin. Disruption of this disinhibition can cause abnormal dopaminergic neurotransmission of striatal neurons (Fienberg, et al., 1998). Together with protein kinases (e.g., PKA, PKC, CaMKII and MARCKS) calcineurin regulates neuronal cytoskeleton proteins for activity-dependent adaptations of dendritic spine density (R. Groth, et al., 2003). Decreased calcineurin activity has been proposed to cause abnormality of microtubule-associated proteins typical for Alzheimer's disease (Q. Lian, C. Ladner, D. Magnuson, & J. Lee, 2001). In addition to regulating the functions of pre-existing proteins for the rapid induction of neuronal adaptation, calcineurin is also involved in the regulation of transcription and *de novo* protein synthesis. Calcineurin-mediated disinhibition of PP1 prevents CREB activation by weak synaptic stimulation protecting from long-term changes in neuronal function induced by random-signalling (R. Groth, et al., 2003). Cooperatively with mitogen-activated/extracellular-regulated protein kinase (MAPK/ERK) or PKC, calcineurin activates NFAT-dependent transcription and also contributes to the regulation of inositol 1,4,5-triphosphate (IP3) type 1 receptor expression (R. Groth, et al., 2003).

c-Fos

The activity-dependent transient transcription of the IEG *c-Fos* can be induced within 5min of the onset of neuronal activity (Flavell & Greenberg, 2008). CNS-specific knockout of *c-Fos* can impair long-term memory and NR2A-type NMDA receptor-dependent synaptic plasticity (Fleischmann, et al., 2003). The *c-Fos* promoter contains cis-acting calcium response elements (CREs) and serum response element (SRE). CRE3 is the binding site for the Ca^{2+}/cAMP-regulated transcription factor CREB. SRE is required for serum- and calcium-dependent *c-Fos* expression and contains the binding sequences for the serum response factor (SRF) and Ets-like transcription factor 1 (Elk-1) (Flavell & Greenberg, 2008). SRE binding SRF and Elk-1 as well as binding SRF and other ternary factors[25] can form a stable ternary complex to induce maximal Ca^{2+}-dependent transcription (Flavell & Greenberg, 2008). c-fos together with Jun protein isoforms builds transcription-regulating activator protein 1 (AP-1) complexes that are important for the expression of several DRGs involved in neuronal survival, structural and functional neuroplasticity (Wu, et al., 2004).

Homer1

The mammalian *Homer1* gene can be transcribed as neuronal activity-inducible IEG, such as Homer1a, but also as continuously expressed isoforms, such as Homer1c (K. Szumlinski, et al., 2006). The various Homer1 isoforms are expressed within PFC, striatum, nucleus accumbens, ventral tegmental area, thalamus, parietal cortex, amygdala and hippocampus (K. Szumlinski, et al., 2006). All Homer1 protein isoforms contain the Ena/VASP Homology 1 (EVH1) domain[26] at the amino-terminus (Xiao, et al., 1998). However the activity-dependent Homer1 isoforms lack the coiled-coil (CC) motif at the carboxy terminus of constitutively expressed Homer1 protein isoforms (K. Szumlinski, et al., 2006; Xiao, et al., 1998). Homer1 isoforms bind and regulate several Ca^{2+}-signalling proteins via their EVH1 domain, e.g.

[25] Ternary factors form three-molecule complexes.
[26] The EVH1 domain binds proline-rich sequences acting as molecular adaptor.

mGluRs, Shank (NMDAR-scaffolding protein) and IP_3Rs (Worley, et al., 2007). Homer1 isoforms with CC domain can bind with each other, form isoform-specific multimers and thus act like a bimodular adapter to crosslink or couple proteins together for their interaction in PSD signalling complexes (Worley, et al., 2007; Xiao, et al., 1998). This adapter function of Homer1-CC-isoforms has been shown to facilitate glutamate-mediated excitatory signalling (Fagni, Worley, & Ango, 2002; Xiao, et al., 1998). The competitive binding of Homer1a disrupts CC-Homer1 mediated interactions, which alters the molecular content of the PSD and reduces density and size of dendritic spines (Sala, et al., 2003). Homer1a transcripts are increased within the cortico-limibic-striatal circuit by psychotropic agents (alcohol, cocaine) and stress (K. Szumlinski, et al., 2006). Reintroduction of Homer1a expression in PFC reverses the heightened behavioural response to stressors in *Homer1* knockouts while restoration of CC-Homer1c isoform increases these effects (K. Szumlinski, et al., 2006). CC-Homer1c isoform expression in PFC has been shown to regulate basal glutamate levels and to be critical for working memory and regulation of the emotional response to novelty (Lominac, et al., 2005). Overexpression of IEG-Homer1a in hippocampus impaired working memory task performance (Klugmann, et al., 2005). These findings suggest that IEG-Homer1a transcription within the cortex supports stress resistance and reduces cognitive performance (K. Szumlinski, et al., 2006). Conversely, the expression of the CC-Homer1c isoform decreases the adaptability to stressors and enhances performance in tasks requiring attention and working memory (K. Szumlinski, et al., 2006), which may reflect reciprocal inhibition of adaptations mediated by Homer1 isoforms related to stress and learning. Stress adaptation may require reduced attention to stress-related signals and thus may prevent increased attention required for learning. Behavioural abnormalities, dysregulation of prefrontal glutamate transmission in *Homer1* knockout mice (K. Szumlinski, et al., 2005) and genetic variation in human *Homer1* (Norton, et al., 2003) have all been linked to schizophrenia.

MAPK/ERK

The mitogen-activated/extracellular-regulated protein kinase (MAPK/ERK) signalling cascade is one family of the MAPK superfamily (other MAPK families are c-Jun N-terminal kinases and p38MAPKs) (Adams & Sweatt, 2002). Activation of the ERK pathway can be triggered by numerous extracellular signals, e.g. growth factor receptors, dopaminergic D2 receptors, voltage-gated calcium channels, AMPA and NMDA receptors (Adams & Sweatt, 2002). The ERK pathway is organized around the Ca^{2+}/growth factor dependent protein kinase kinase kinases Raf-1 and B-Raf (Sweatt, 2001). Each of the two can phosphorylate the kinase kinase MAPK/ERK kinase (MEK) isoforms 1-4 (Sweatt, 2001). MEK activates the MAPK/ERK kinase isoforms 1 and 2 by threonine and tyrosine residue phosphorylation (Sweatt, 2001). The activation of ERK isoforms contributes to the regulation of the voltage-dependent K^+ channel $K_V4.2$, cytoskeletal proteins (e.g. MAP-2 and Tau), transcription factors (e.g. Elk-1 and CREB) and signalling proteins (e.g. phospholipase A2, ribosomal S6 kinase, mitogen- and stress-activated kinases) (Adams & Sweatt, 2002; Thomas & Huganir, 2004). ERK signalling is necessary but insufficient for hippocampal and cortical LTP, can drive CaMKII-mediated insertion of AMPA receptors and regulate dendritic spine numbers (Thomas & Huganir, 2004). ERK signalling thus contributes to synaptic plasticity and learning via the integration of neuronal input and the coordination of neuronal adaptations.

Methyl-CpG Binding Protein 2

The neuronal activity-regulated transcription regulator Methyl-CpG Binding Protein 2 (MeCP2) binds methylated CpG dinucleotids of target genes (e.g., in promoter of *BDNF* and *CRH*) and unmethylated four-way DNA junctions (Chahrour & Zoghbi, 2007; S. Cohen & Greenberg, 2008). Binding of MeCP2 recruits DNA and histone methyltransferase, complexes of chromatin-remodelling enzymes, transcription factors and corepressors (Sin3A and histone deacetylases 1 and 2) for chromatin condensation and transcriptional repression

(Chahrour & Zoghbi, 2007). Ca^{2+}-dependent phosphorylation of MeCP2 by CaMKII releases MeCP2 from the promoter disinhibiting BDNF transcription (W. Chen, et al., 2003) with effects on spine and dendrite development. MeCP2 thus participates in both arrest and induction of target gene transcription. Cooperation between MeCP2, CREB and MEF2 to recruit CBP to BNDF promoter IV could initiate BDNF transcription (Chahrour, et al., 2008). Alternative splicing of exons leads to two MeCP2 isoforms (Chahrour & Zoghbi, 2007). The highly conserved 3'UTR contains multiple polyadenylation sites for alternative mRNA processing generating four different MeCP2 transcripts (Chahrour & Zoghbi, 2007). MeCP2 interacts with RNA and could be involved in RNA splicing (Chahrour & Zoghbi, 2007). MeCP2 is involved in the regulation of excitatory and inhibitory synapses, LTP and synaptic plasticity in cortex and hippocampus and hippocampal short-term synaptic depression (Asaka, Jugloff, Zhang, Eubanks, & Fitzsimonds, 2006; Chao, Zoghbi, & Rosenmund, 2007; Dani, et al., 2005; Moretti, et al., 2006; Nelson, Kavalali, & Monteggia, 2006).

Myocyte Enhancing Factor 2

MEF2 activates its target genes by coordinating the regulation of chromatin structure and function of transcription factors (S. Cohen & Greenberg, 2008). The activity-induced, Ca^{2+}-dependent dephosphorylation of MEF2A by calcineurin and subsequent switch from sumoylation to acetylation disrupts MEF2's interaction with histone deacetylases. This in turn, induces the transcription of IEG *Nur77* (activity-regulated IEG transcription factor that regulates cell survival and growth) that restricts dendritic claw differentiation in granule neurons of the cerebellum (Shalizi, et al., 2006). In hippocampal neurons, glutamatergic synaptic activity induces calcineurin-mediated dephosphorylation MEF2A and MEF2D that activate transcription of *Arc* and *synaptic Ras guanosine triphospatase activating protein* (*synGAP*) restricting synapse number (Flavell, et al., 2006). MEF2 is also one of the regulators of *neurotrophin-3* (*NT-3*) transcription that mediates BDNF-induced neuronal

survival (Shalizi, et al., 2003). MEF2 has furthermore been suggested to regulate spine density and Akt/PKB signalling in response to activation of voltage-gated Ca^{2+}-channels or D1 receptors in spines of the nucleus accumbens (Pulipparacharuvil, et al., 2008). These effects are mediated by MEF2-regulated genes that encode regulators of cytoskeletal proteins and the expression PI3-kinase (Pulipparacharuvil, et al., 2008).

Nuclear factor of Activated T-cells

The Ca^{2+}-signalling-dependent regulation of the nuclear translocation of NFAT represents a mechanism by which neuronal activity can regulate gene expression (I. A. Graef, et al., 1999). Deficient calcineurin-NFAT signalling impairs neurotrophins and netrin-dependent axon outgrowth (I. Graef, et al., 2003). Neurotrophins induce calcineurin activity to dephosphorylate NFAT for its translocation into the nucleus and activation of NFAT-dependent transcription of e.g. the IEG *Nur77* (I. Graef, et al., 2003). NFAT-dependent transcription is terminated via its phosphorylation by nuclear kinases, which induces its translocation to the cytoplasm. Conditions that activate Akt/PKB inhibit glycogen synthase kinase-3 (GSK3) extending the nuclear presence of NFATs (Benedito, et al., 2005). NFAT3-dependent transcription promotes neuronal survival and can protect granule neurons from the apoptotic effects of serum or K^+ deprivation, presumably by its influence on the transcription of pro-survival genes (Benedito, et al., 2005). In hippocampal pyramidal neurons BNDF through TrkB-signalling has been shown to activate the NFAT-dependent transcription of the genes encoding IP_3R1 and BDNF (R. D. Groth & Mermelstein, 2003). NFAT-dependent transcription of IP_3R1 and GluR2 genes is also initiated by D1 receptor-mediated enhancement of calcium entrance through L-type channel in striatal neurons (R. D. Groth, et al., 2008).

Nerve Growth Factor-Inducible protein A

Transcription of the IEG *NGFI-A* encoding the transcription factor NGFI-A can be induced in response to neuronal activity or neurotrophic factors (Knapska & Kaczmarek, 2004). Activation of CREB, SRF (Serum Response Factor) and Elk-1, which can bind to the *NGFI-A* promoter elements CRE (Calcium Response Element) and SRE (Serum Response Element), by MAPK/ERK pathway can up-regulate the transcription of *NGFI-A* (Knapska & Kaczmarek, 2004). Additional response elements in the promoter exist for the transcriptional regulation of *NGFI-A* by e.g., estrogen (Slade & Carter, 2000), auto-regulation by NGFI-A (Sakamoto, et al., 1991; Schwachtgen, Campbell, & Braddock, 2000) and inhibition by e.g., NGFI-A binding protein 1 (NAB1) (Russo, Sevetson, & Milbrandt, 1995). Temporal and local regulation of NGFI-A mRNA and protein expression contribute to the transcriptional regulation of multiple DRGs (Knapska & Kaczmarek, 2004) encoding e.g., glucocorticoid receptor (GR) gene (*NR3C1*) (Weaver, et al., 2004) and the synaptic vesicle-cytoskeleton-associated proteins synapsin I/II (Thiel, 1993). NGFI-A also interacts with several other transcription factors like, CBP (Silverman, et al., 1998), c-Fos (Dragunow, Tse, Glass, & Lawlor, 1994; Gius, et al., 1990) and NGFI-B (G. Williams & Lau, 1993). NGFI-A protein is expressed throughout the brain e.g., in thalamus, hypothalamus, striatum, amygdala, hippocampus and sensory cortices (Knapska & Kaczmarek, 2004). Up-regulation of *NGFI-An* expression in sensory cortices has been observed in response to sensory stimulation e.g., through environmental enrichment (Pinaud, et al., 2002; C. Wallace, et al., 1995). However the regulation of *NGFI-A* expression is influenced by a large spectrum of stimuli including stress, seizures, hippocampal LTP-inducing stimuli and various types of learning (Knapska & Kaczmarek, 2004).

miR-134

One of the BDNF-regulated mRNAs that contains a binding site for miR-134 within its 3'UTR is LIM-domain containing protein kinase 1 (Limk1) (Schratt, et al., 2006). Binding of miR-134 contributes significantly to the reduction of Limk1 mRNA translation thereby reducing Limk1 protein levels at synapses unless BDNF cancels these effects (Schratt, et al., 2006). Limk1 targeted to excitatory postsynapses within dendrites of hippocampal neurons regulates actin filament dynamics, and decrease of Limk1 protein reduces dendritic spine size (Schratt, et al., 2006). Thus, BDNF promotes and miR-134 inhibits dendritic outgrowth that depends on Limk1 protein levels.

miR-132

The transcription of *miR-132* is predominately initiated by neuronal activity-dependent CREB binding to the *miR-132* promoter (Wayman, Davare, et al., 2008). Binding of miR-132 to a cis-acting element within the 3'UTR of p250GAP down-regulates the translation of p250GAP (Wayman, Davare, et al., 2008). The reduction of PSD protein p250GAP levels attenuates its inhibitory effects on Rho family GTPases like Rac (Wayman, Davare, et al., 2008). Reduction of p250GAP leads to dendritic growth that could be mediated by increased Rac activity or interactions of p250GAP with other post-synaptic proteins like, NMDA NR2B receptor subunit, scaffold protein PSD-95 and β-catenin (Wayman, Davare, et al., 2008). Moreover, miR-132 binding to a cis-acting element within the long 3'UTR transcript of MeCP2 decreases MeCP2 protein level in cultured cortical neurons (Klein, et al., 2007).

Future research directions on genes, brain and behavioural adaptability

How can genome output regulation interact with adaptation mechanisms at the behavioural level?

The interaction of an individual with its environment can induce changes at the genome level, which in turn can induce changes of the individual's behaviour. One example is the naturally occurring variation in the degree of maternal care (grooming and nursing behaviour of rats) that has been shown to regulate the expression of the glucocorticoid receptor (GR) gene (*NR3C1*) in the hippocampus of rat pups (Weaver, 2007; Weaver, et al., 2007; Weaver, Meaney, & Szyf, 2006). The genome configuration is regulated via acetylation/ deacetylation of specific histones and sequence methylation/ demethylation on the NGFI-A transcription factor response element of the GR promoter. The methylation status of this promoter sequence appears to be mediated through serotonin signalling at hippocampal 5-HT_7 receptors activated in response to maternal care. Thus the regulation of the IEG *NGFI-A* expression depends presumably on neuronal activity induced by the dam-pub interaction. Additional activity-dependent transcription factors and cofactors are also likely to participate in the regulation of GR gene transcription. Depending on its histone(s) acetylation status and its methylation status the transcription factor NGFI-A can bind to this element in the GR promoter sequence. NGFI-A binding regulates the transcriptional activity of the GR gene and thus alters the expression of hippocampal glucocorticoid receptor levels. The transcription of *NGFI-A* is correlated with maternal care-induced GR gene expression in the hippocampus (Weaver, et al., 2007). The early-life maternal care-induced methylation status of the promoter sequence has been shown to persist and influence behaviour and hypothalamic-pituitary-adrenal stress response of the offspring in adulthood and to be reversible with cross-fostering (Fish, et al., 2004; Weaver, et al., 2004). The offspring of dams exhibiting a high degree of maternal care showed enhanced learning, memory, and exploratory behaviour and less stress reactivity. Apart from this intriguing interaction between genomic adaptability via epigenetic regulation and behavioural variability, epigenetic regulation has also been suggested to influence the expression of genes implicated in psychopathologies like schizophrenia (Abdolmaleky, et al., 2004; Gräff & Mansuy, 2008; Tsankova, et al., 2007).

The heterogeneity of complex psychiatric disorders like schizophrenia is best accounted for by multi-factorial models that incorporate genetic, epigenetic and environmental influences. The dysregulation of gene expression, intra-and extraneural signalling pathways, neural and neural network properties and behaviour are common features of complex psychiatric disorders (McClung & Nestler, 2008; Ramocki & Zoghbi, 2008; Ross, et al., 2006). Responsiveness of these adaptation mechanisms to environmental factors and their role in neurodevelopment and neuroplasticity could also explain the impact of stress, drugs, infections, etc. in the manifestation of the genetic propensity to psychiatric disorders. For these reasons the dysregulation of adaptation mechanisms could be the common aspect of these disorders.

What factors contribute to interindividual variability in neural and cognitive functions?

Genetic interindividual variability contributes significantly to interindividual variability in cognitive functions (Ando, et al., 2001; Blokland, et al., 2008; C. Wolf, et al., 2009) and to complex neuropathologies (Owen, Williams, & O'Donovan, 2004a; Prathikanti & Weinberger, 2005; Ross, et al., 2006). Individual genetic variability is thus a key factor for the understanding of individual differences in behavioural or cognitive performance measures and their neurophysiological correlates. However, as described above genetic variability interacts with epigenetic variation and a large variety of regulatory factors that can mediate environmental influences.

The total interindividual variability of the genome sequence in humans is estimated at 0.2% of which 40% are nucleotide variations (SNPs) and 60% structural changes (Sebat, 2007). Structural variations contribute presumably at least 20% to the variability of gene expression (Hurles, Dermitzakis, & Tyler-Smith, 2008). Only a small proportion of the total DNA sequence variability will alter protein coding sequences (Venter, et al., 2001) because these make up only about 2-3 % of the humane genome (J. Mattick, 2001). Most of the variability

thus affects genome sequences that are transcribed into ncRNAs (J. Mattick, 2001) and untranscribed sequences that are presumably also regulatory. Adaptively evolving loci have been identified in non-coding sequence of the human genome that may also affect neuronal regulatory regions (Kelley & Swanson, 2008). Genetic and also epigenetic variation within regulatory non-coding sequence is expected to be the major site for genetically-driven individual differences and in addition interacts with environmentally-driven regulation. Changes in regulative ncRNA sequences could result in subtle changes that contribute to interindividual variability of quantitative traits (J. Mattick & Makunin, 2006). In addition comparative genome analysis has revealed that most evolutionary conserved sequences in mammalian genomes are non-coding sequences and not genes (Lindblad-Toh, et al., 2005). These non-coding sequences are often found close to genes that encode transcription factors (Canestro, Yokoi, & Postlethwait, 2007) and often contain cis-acting regulatory elements that regulate the transcription of adjacent genes (Woolfe, et al., 2005). Through its cis- and trans-acting effects, non-coding sequence is involved in gene and protein regulation. The variation and conservation of non-coding sequence may thus reflect its role in the diversification and maintenance of phenotypes during evolution. Most genes give rise to multiple mRNA transcripts for the regulation of translation to adapt the isoform, quantity or location of protein. Differences in the 3' and 5'UTRs are critical for mRNA processing as well as timing and location of translation via interaction with transacting factors. For example cytoplasmatic polyadenylation element binding protein 1 (CPEP1) is part of a multiprotein complex that binds to specific cis-acting elements of the 3'UTR to regulate mRNA transport, polyadenylation and translation of several synaptic plasticity proteins (Wayman, Lee, et al., 2008). The length of 3'UTR sequence of BDNF mRNA is thus important for the regulation of its transport, which has been shown to affect spine morphology and synaptic plasticity in hippocampal neurons (An, et al., 2008). 3'UTR removal of α-CaMKII mRNA prevents its translocation, reduces protein expression in PSD, late-LTP stability and memory (Wayman,

Lee, et al., 2008). 3'UTR cis-acting elements signal the dendritic localization and translation of α-CaMKII mRNA (Mayford, Baranes, Podsypanina, & Kandel, 1996; Mori, Imaizumi, Katayama, Yoneda, & Tohyama, 2000). miRNA expression also modulates synaptic plasticity and can regulate translation in the human brain by interacting with target gene sequences in 3'UTR (R. Zhang & Su, 2008). The variation of miRNAs themselves and their target gene sequences may increase variability in gene expression and thus influence phenotypic adaptability (R. Zhang & Su, 2008).

In summary proteins and ncRNAs that regulate neuronal adaptation integrate genetic, epigenetic and extracellular signals within intracellular signalling networks. Genetic and epigenetic changes in regulatory non-coding sequences of regulators and their targets, (e.g. in cis-elements of promoters and UTRs, cis-and trans-elements of regulatory proteins and ncRNAs) can alter neuronal adaptation. Furthermore such alterations can interact with environmental factors. We expect that future research into variation within regulatory non-coding sequences of proteins and ncRNAs involved in the regulation of neuroplasticity will explain individual differences and impairments in learning and memory and complex psychiatric phenotypes.

How can genetically-driven alternations of brain function and behaviour be detected?

Methods interconnecting neuro-molecular, neuro-physiological and behavioural levels can reveal the impact of genetic variability to variations of brain functions and behaviour. One technique with the capacity to cover this spectrum of functions is genetic neuroimaging, which combines neuroimaging technologies such as fMRI with molecular genetics. However this technique is limited by two major constraints. First the analysis is restricted to DNA sequence variations because the genome is isolated from lymphocytes or other dispensable cells. For this reason genetic neuroimaging cannot provide information about the genome output variation in neurons. BOLD-MRI/fMRI can localise and quantify the change of the

haemodynamic signal at neural network level. By modelling the time course of the signal change as a function of the behavioural manipulation, e.g. a memory task, this method provides a correlate of task-related neural activity. This, points to the second main limitation, which is the correlative nature of genetic neuroimaging. Knowledge regarding the effects of genetic variants on expression and function of neuronal activity-regulated proteins and ncRNAs is thus a prerequisite to validate the results of genetic neuroimaging. Common genetic variants known to affect the expression or function of neuronal activity-regulated proteins and ncRNAs involved in neuroplasticity are rarely known, but might be found in non-coding regions. So far the genetic contribution to individual variation of neuronal network activity involved in cognitive functions has been investigated for genes encoding receptors or enzymes of several neurotransmitter systems as well as BDNF (Egan, et al., 2003; T. Goldberg & Weinberger, 2004). The strengths of fMRI are its high sensitivity and reasonable spatial resolution. Moreover, the correlation between genetic and task-related imaging and performance data allows for the validation of effects across functional levels. This non-invasive but physiological approach may help to quantify and specify the influence of genetic parameters on brain functions and behaviour. Ultimately genetic neuroimaging would allow monitoring of not only a signal change dependent on the manipulation of behaviour but also a signal change dependent on genome output variation. Advanced invasive methods of neurogenetic activity imaging like catFISH (cellular compartment analysis of temporal activity by Fluorescent In-Situ Hybridization) can localise, quantify and identify mRNAs and proteins within neuronal networks activated for distinct stages of learning and memory (Guzowski, et al., 1999; Miyashita, et al., 2008). Another invasive way to investigate *in vivo* molecular changes involved in the regulation of neuronal activity, synaptic and neuronal plasticity, e.g. the regulation of IEG expression at the network level is the transgenic or viral-introduction of neuronal activity fluorescent sensors (Barth, 2007). However, non-invasive *in vivo*-techniques will be necessary to study neuronal activity and plasticity-related

genome output regulation during cognitive activities in humans. Presently we will have to combine insights from invasive and non-invasive approaches in order to investigate the integration of adaptation mechanisms across functional levels. Only by understanding these interactions will we elucidate the interplay between genome, epigenome and environment for human behavioural adaptability and thus individuality. Furthermore without understanding the integration of adaptive mechanisms across the behavioural, neural network, cellular and molecular level we will not be able to answer questions about cognitive functions such as what are the biological mechanisms that differentiate working memory and long-term memory.

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General Conclusion

First, we demonstrated that genetic imaging is a promising non-invasive technique to investigate the contribution of genetic effects to human interindividual differences in cognitive functions. Our experimental findings added to the knowledge about the potential impact of individual genetic variability in an important synaptic regulatory protein (dysbindin-1) on working memory (WM) for emotional faces.

Second we aimed to investigate the dysbindin-1 genotype effect on performance for emotional face WM and the related brain activity in patients with schizophrenia. As we expected the majority of our patients (seven out of eight) carried the schizophrenia risk-associated dysbindin-1 genotype (data not presented). This is due to the fact that the risk associated allele (A = .87 (Bray, et al., 2005)) is common in the general population as is the case for the majority of alleles associated with the risk for schizophrenia (Purcell, et al., 2009) but appears to be particularly so in the case of *DTNBP1* (Riley, et al., 2009). The risk that is conferred by these common alleles is very small (1.1-1.5) thus explains only a small proportion of heritable risk (Manolio, et al., 2009) and implies that the number of common risk contributing variants is very large. Indeed new evidence suggests that common polygenic variants contribute at least one third of the total risk for schizophrenia (Purcell, et al., 2009). Interestingly more than 80% of variants associated with complex diseases fall inside non-coding regions emphasizing the importance of variability outside genes (Manolio, et al., 2009).

Our results support the conclusion that variations in non-coding sequence may be important to explain individual variability in cortical and neurocognitve functions in particular if such variants affect the expression of regulators involved in neuroplasticity (including regulatory ncRNAs, proteins, e.g. dysbindin or activity-regulated proteins).

Despite every effort made to recruit the number of patients needed for sufficient power to test our hypothesis about the dysbindin-1 genotype effect on emotional face WM, we failed to obtain the aimed for sample size of 30 patients. Advantageously, the small group of patients analysed, was exceptionally homogenous showing only mild cognitive impairments. For these reasons we reduced the number of variables in our design (excluding the genotype) and focused on brain activity differences related to accurate WM performance between patients and matched healthy participants. Our results suggest that highly functional patients achieve correct WM performance because they utilise compensatory adaptations to cope with pathological changes. Future investigations that address the regulation of these adaptations may reveal new therapeutic interventions, e.g. the selective enhancement of brain activity through neurofeedback provided by fMRI.

Finally we introduced the concept of adaptability to connect the molecular, cellular, neural network and behavioural levels. Then we reviewed the regulation of adaptation mechanisms that depends on the integration of genetic, epigenetic and environmental factors across functional levels. We discussed why the investigation of adaptation mechanisms across functional level is needed to answer complex questions in cognitive and clinical neuroscience. For example questions about the basis of interindividual differences in cognitive functions, and dysfunctions observed in psychiatric disorders as well as the dissociation between cognitive functions.

Limitations and future directions

A larger sample including 100 participants or more in the control group and particularly a much larger patient sample would have allowed to include more independent variables for example to extend the number of genes for the investigation of interaction effects between genes and genes and environmental factors. Furthermore it would have been interesting to investigate haplotypes instead of focusing on single nucleotide polymorphisms. We also did

collect serum samples of all participants, which are not yet analysed. Analysis of these samples could be used to correlate e.g. the protein profiles or concentration of specific neurotransmitter metabolites or hormones (at least in the male participants) with the genetic data.

Most previous genetic imaging studies have detected genotype effects with small to medium effect sizes using sample sizes of 20-40 participants (A. Meyer-Lindenberg & D. R. Weinberger, 2006; Munafo, Brown, & Hariri, 2008). In particular fMRI has been suggested to exhibit more power to detect genetic effects in smaller samples compared with other more complex phenotypic measures (Egan, et al., 2003). A study that investigated the false positive rates in genetic imaging suggested appropriate control of type I errors by standard false discovery correction methods but testing of more than one SNP would require additional correction (A. Meyer-Lindenberg, et al., 2008). Sizes of genetic effects also depend on the targeted endophenotype, the reliability and strength of the imaging signal elicited by the paradigm, confounding factors and data analysis (A. Meyer-Lindenberg & D. R. Weinberger, 2006). We detected in our study medium effects concordant with previous reports. In order to increase the power and include more genetic (GWAS) and other variables in genetic imaging studies larger samples (N=500-1000) and more sophisticated data analysis techniques are required (de Geus, Goldberg, Boomsma, & Posthuma, 2008; Potkin, et al., 2009). A new approach uses the differences in imaging data between cases and controls (or grouping according to other criteria) to explain genetic variability between groups instead of asking whether genetic variability explains variability in the imaging data (Potkin, et al., 2009). This allows the genome-wide discovery of genetic variants associated with imaged or otherwise quantified endophenotypes.

The more information is available about the functional significance of a genetic variant the more likely are consistent findings, the easier their interpretation and the less likely are

spurious associations (Perneger, 1998). With our approach of genetic imaging we focused thus on neurobiological plausibility when selecting the investigated genetic variants (e.g., genes known to be expressed in the brain, genetic variants preferentially associated with gene/protein expression or function, involved in functional/ structural neuroplasticity, likely to be expressed in regions commonly activated by WM/emotion tasks/face processing, likely to influence these cognitive functions and likely to be involved in susceptibility to schizophrenia) based on previous research as opposed to more explorative studies where such prior knowledge is unavailable. This biased our selection towards well-studied genes with respect to their putative involvement in these brain functions and schizophrenia. Associations between cognitive functions and most of the genes selected had previously been found with neuroimaging (*COMT*, *SLC6A*, *DTNBP1*, *RGS4*, *GAD1*) or/and cognitive tests in humans (*DTNBP1, COMT, SLC6A, NRG1, GAD1*) or animal studies (*NRG1, GRIN1, DTNBP1, COMT, SLC6A*). *COMT, DTNBP1, NRG1* had been linked with schizophrenia based on the convergent findings of statistical significance, reproducibility of associations, animal models and human endophenotype studies (Gogos & Gerber, 2006). More recently a systematic meta-analyis of genetic candidate genes for schizophrenia found strong significant effects for 16 genes including *DTNBP1, COMT, SCL6A* and *GRIN2B* (Allen, et al., 2008). Our selection criteria thus merged statistical and neurobiological evidence although we did not systememattically quantify or qualify these criteria. We were further constrainted by the relatively small number of selected variants, commoness of minor alleles (frequency > .10) both owed to the size of our sample and available genotyping resources.

Even with biological evidence being available the selection of genetic variants remains difficult because there is a multitude of interacting factors (genetic, epigenetic and environmental) that may blur individual effects, evidence from association studies is often inconsistent with respect to the effect sizes, specific genes, variants and alleles associated and no rule or established way exist to guarantee success. For genetic imaging we think it is

helpful to have background information on the neurobiological and cognitive plausibility of variants in order tailor the paradigm and method of analysis to the variants investigated. For example does the task activate areas of the brain that have shown differential expression or function of the product influenced by this genetic variant? Despite all these information being available in the case of the COMT and 5-HTT polymorphisms, which we did select in particular because of their potential effects on emotion processing and working memory, we were unable to replicate these earlier findings in our large control sample. Future selection may be facilitated using Bayesian approaches that allow the quantification of the prior probability of genetic variants. Also the analysis of interactions of a suspected gene/protein with other genes/proteins through signalling pathways like the one available for dysbindin-1 (Guo, et al., 2009) may deliver new testable hypothesises. A priori genetic variants may also be identified through the analysis of interactions across functional levels that may converge on a limited number of genes that at the same time may reveal new testable endophenotypes.

Choosing rare variants with large frequency differences (controls/ patients) is not useful for the genetic imaging approach if one relies on opportunistic-sampling, relatively small sample size </=100 (cost-effectiveness) because the likelihood to get carriers with the rare allele is very low. We selected one variant with a minor allele frequency below 10% (GRIN1 rs11146020) for which we found no significant effects on behavioural measures in the control sample. Rare variants are problematic if one relies on opportunistic-sampling and relatively small samples (n<100). Provided that numbers of rare allele carriers are sufficient (family-studies or very large samples) and effects are large enough, rare variants can be investigated with genetic imaging. Presently genetic imaging studies for rare variants like copy number variation are still rare (K. P. Lesch, et al., 2010). The individually rare and highly penetrant copy number variations (chromosomal deletion and insertions) that may contribute to the genetic risk of schizophrenia particularly in spontaneous cases (B. Xu, et al., 2008) appear to be different between individuals, families and subpopulations (Tam, Redon,

Carter, & Grant, 2009). These mutations are more difficult to detect and verify because they are rare, can occur *de novo* and throughout the genome affecting many different genes. The excess of CNVs was found to be small comparing patients with schizophrenia and controls (Delisi, 2009). At present it remains unknown whether they would be sufficient to explain the genetic predisposition in all cases of schizophrenia (Delisi, 2009). However structural genome changes are an important source for interindividual variability in health and disease (Sebat, 2007; H. J. Williams, et al., 2009).

Apart from genetic imaging using fMRI numerous other imaging techniques including structural imaging (Ohnishi, et al., 2006), EEG (Fallgatter, et al., 2006), DTI (McIntosh, et al., 2008) and MEG (Ahveninen, et al., 2006) have been applied for the investigation of genetic influences on brain function and structure. As already pointed out above, because of the correlative nature of genetic neuroimaging the validation of results depends on convergent findings from studies applying invasive techniques, and are less dependent on modelling of data. Without the information provided by post-mortem and animal and cell culture studies we would not have been able to interpret our findings.

Recently such studies provided new insights about the interactions between genes, neurons and behaviour by showing neuronal activity-dependent initiation of new gene transcription. This is required for *de novo* protein synthesis that plays an important role in LTP and structural plasticity (Bramham, 2008).

In vitro studies that use florescence makers to trace gene expression in combination with electrophysiology, e.g. by time-lapse live-cell fluorescence imaging can identify neuronal activity-dependent changes in gene transcription (Kawashima, et al., 2009).

The investigation of these mechanisms is crucial because they are involved in the regulation of neuroplasticity, such as neuronal activity-dependent synapse number (Flavell, et al., 2006), dendritogenesis (Fiore, et al., 2009) or adult hippocampal neurogenesis (Ma, et al., 2009). Genetic manipulation of activity-dependent transcription factors that induce the transcription

of immediate early genes (IEGs) has been shown to impair learning and memory through their effects on structural synaptic plasticity (Barbosa, et al., 2008). Impairments in these neuronal activity-dependent regulation mechanisms have been linked to genetically complex mental disorders (Swanberg, Nagarajan, Peddada, Yasui, & LaSalle, 2009). The regulation of activity-dependent gene expression has also been shown to play an important role during the development of GABAergic synapses (Y. Lin, et al., 2008), which could be relevant for the pathogenesis of schizophrenia. Neuronal activity-responsive IEGs and their transcription factors are expressed in regions important for emotion and cognition such as prefrontal, orbital frontal, occipital cortex, hippocampus and amygdala.

Genes make up only about 1.06% of human DNA (compared to 1.27% genes in mouse DNA) (Church, et al., 2009), the rest is non-coding sequence that is likely to play an important regulatory role for the adaptive use of genes (in particular the regulation of gene expression). This suggests that variations in sequences for how proteins are build may be less relevant for phenotypic differences than variations in sequences for how genes and proteins are used (where, when, how much, in what form and function), not to mention epigenetic variability (Cubas, Vincent, & Coen, 1999). At present the effects of genetic variability in non-coding sequence on the expression of neuronal activity-regulated non-coding RNAs or regulatory proteins are largely unknown. But recent evidence suggests the importance of non-coding sequence for cis- and trans-binding interactions between RNAs and RNAs and proteins during the regulation of gene expression (X. Wang, et al., 2008). Variability in non-coding sequence that affects regulation of gene expression has been related to psychiatric disorders (Zhao, et al., 2009), normal variation of cognition (Gosso, et al., 2008), emotional and social behaviours (Hammock, Lim, Nair, & Young, 2005).

Hence it would be interesting to investigate variability particularly in non-coding regulatory sequences (e.g. UTRs) of these synaptic activity-regulated genes/ proteins with genetic neuroimaging also with respect to schizophrenia. Another interesting target, for future genetic

imaging studies are activity-regulated microRNAs that are like IEGs expressed in response to synaptic activity and regulate the translation of synaptic proteins involved in structural plasticity (Vo, et al., 2005; Wayman, Davare, et al., 2008). Because these micro-RNAs, transcription factors and proteins that are expressed or regulated in response to neuronal activity regulate synaptic proteins involved in functional and structural adaptations of neurons, genetic variation that affects these regulators may contribute to interindividual variability in cognitive functions as well as their dysfunction in disorders like schizophrenia.

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I would like to dedicate this thesis to radioeins in Potsdam– Nur für Erwachsene. http://www.radioeins.de/programm/index.html

Supplemental material for experimental chapter I

Suppl. table 1a. Brain regions significantly higher activated for angry compared to neutral faces at α-level .05 and voxel threshold of 200 voxels for 56 control participants.

Brain region	Talairach coordinates			cluster size in voxels/ mm^3
	x	y	z	
Left fusiform face area	-37	-50	-14	1137
Left globus pallidus	-21	-4	-1	601
Left hippocampus	-20	-27	-4	211
Left inferior temporal gyrus	-42	-34	-23	636
Left insula	-26	2	-8	2602
Left occipital cortex	-31	-82	-7	285
Left occipital face area	-33	-73	-10	377
Left substantia innominata	-21	-6	-6	1593
Left ventrolateral prefrontal cortex	-46	29	14	1744
Right amygdala (extended)	21	-2	-11	2107
Right caudate nucleus	16	-4	20	364
Right dorsolateral premotor cortex	36	0	39	865
Right fusiform face area	39	-15	-18	2916
Right globus palidus	17	-5	0	609
Right inferior temporal gyrus	44	-37	-22	1980
Right insula	25	11	-11	571
Right intra-parietal lobe	33	-61	41	800
Right intra-parietal sulcus	26	-74	24	422
Right middle frontal gyrus	35	-1	39	525
Right occipital cortex	30	-86	-8	287
Right occipital face area	37	-73	-13	2039
Right orbital frontal cortex	27	38	2	392
Right superior temporal sulcus	55	-52	5	4471
Right ventrolateral prefrontal cortex	49	27	12	5039

Suppl. Table 1b. Brain regions significantly higher activated for happy compared to neutral faces at α-level .05 and voxel threshold of 200 voxels for 56 control participants.

Brain region	Talairach coordinates			cluster size in voxels/
	x	y	z	mm^3
Left amygdala	-18	-7	-20	294
Left entorhinal cortex	-38	-13	-28	419
Left fusiform face area	-37	-52	-13	709
Left inferior frontal gyrus	-42	19	27	1601
Left inferior frontal gyrus	-48	39	10	1426
Left insula	-31	7	-12	4461
Left occipital cortex	-31	-84	-7	3269
Left occipital face area	-31	-76	-12	940
Left substantia innominata	-18	-6	-6	203
Right amygdala	16	-5	-14	313
Right inferior frontal gyrus	44	9	29	829
Right inferior temporal gyrus	47	-33	-22	1450
Right middle temporal gyrus	55	7	-13	1181
Right occipital cortex	30	-84	-8	3873
Right occipital face area	33	-75	-11	2651
Right orbital-frontal gyrus	28	38	0	401
Right ventrolateral prefrontal cortex	48	26	12	2286
Right ventrolateral prefrontal cortex	33	27	-6	289

Suppl. Table 2a. Right FFA significantly higher activated for angry compared to neutral faces, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by *DTNBP1* genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected **pair-wise comparisons**	***t*** (uncorrected for multiple comparisons)	R^2
Emotion *F* (2, 108) 5.88 **	angry 2.18 *	.08
angry vs. neutral **		
Load *F* (3, 162) 9.30 ***	happy 2.41 *	.10
load 1 vs. load 2, 4 ***		
load 1 vs. load 3 **		
Load x *DTNBP1* *F* (3, 162) 3.59 *	neutral 1.79	.06
DTNBP1 *F* (1, 54) 4.72 *		

* $p < .05$, ** $p < .01$, *** $p < .001$

Suppl. Table 2b. Left hippocampus significantly higher activated for angry compared to neutral faces, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by *DTNBP1* genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected **pair-wise comparisons**	***t*** (uncorrected for multiple comparisons)	R^2
Emotion *F* (2, 108) 3.58 *	angry 2.88 **	.13
angry vs. neutral *	happy 2.24 *	.08
DTNBP1 *F* (1, 54) 7.14 *	neutral 2.14 *	.08

* $p < .05$, ** $p < .01$, *** $p < .001$

Suppl. Table 2c. Right OC significantly higher activated for both emotion contrasts, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by *DTNBP1* genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected **pair-wise comparisons**	*t* (uncorrected for multiple comparisons)	R^2
Emotion *F* (2, 108) 10.94 ***	angry 2.76 **	.13
angry vs. neutral *		
happy vs. neutral ***		
Load *F* (3, 162) 4.34 **	happy 2.97 **	.14
load 1 vs. load 2, 3, 4 *		
Emotion x *DTNBP1* *F* (2, 108) 2.45	neutral 2.30 *	.09
DTNBP1 *F* (1, 54) 7.39 **		

* $p < .05$, ** $p < .01$, *** $p < .001$

Suppl. Table 2d. Right OFC significantly higher activated for both emotion contrasts, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by DTNBP1 genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected **pair-wise comparisons**	*t* (uncorrected for multiple comparisons)	R^2
Emotion *F* (2, 108) 2.99	angry 3.16 **	.16
angry vs. neutral $p = .054$		
Emotion x *DTNBP1* *F* (2, 108) 2.79	happy 1.63	.05
DTNBP1 *F* (1, 54) 8.58 **	neutral 2.99 **	.14

* $p < .05$, ** $p < .01$, *** $p < .001$

Suppl. Table 2e. Right ITG significantly higher activated for both emotion contrasts, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by *DTNBP1* genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected pair-wise comparisons	***t*** **(uncorrected for multiple comparisons)**	R^2
Emotion *F* (2, 108) 6.44 **	angry 2.40 *	.10
angry vs. neutral *	happy 2.28 *	.09
happy vs. neutral **		
DTNBP1 F (1, 54) 5.55 *	neutral 1.95	.07

* $p < .05$, ** $p < .01$, *** $p < .001$

Suppl. Table 2f. Right OFA significantly higher activated for both emotion contrasts, activity significantly correlating with task-performance measures and significantly affected by dysbindin-1 genotype.

ANOVA results for main effects of the between-subject factor *DTNBP1* genotype and the within-subject factors emotion and load, their interactions, and post-hoc comparisons	independent samples t-test results for *DTNBP1* genotype effect on beta means for each emotion type (DF = 54) as well as the amount of variability in beta mean for the emotion type explained by *DTNBP1* genotype	
Factor/ interaction *F* (degrees of freedom) or Bonferroni corrected pair-wise comparisons	***t*** **(uncorrected for multiple comparisons)**	R^2
Emotion *F* (2, 108) 10.72 ***	angry 2.65 *	.12
angry vs. neutral ***		
happy vs. neutral **		
Load *F* (3, 162) 7.02 ***	happy 2.72 **	.12
load 1 vs. load 2, 3, 4 **		
Emotion x *DTNBP1 F* (2, 108) 2.52	neutral 1.99	.07
DTNBP1 F (1, 54) 6.14 *	angry-neutral 2.19 *	.08

* $p < .05$, ** $p < .01$, *** $p < .001$

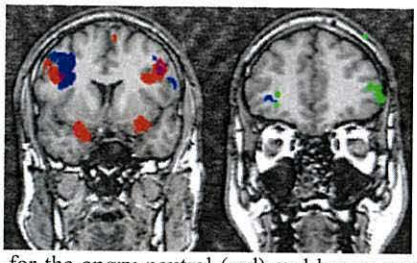

Figure S1. Overlay of the original maps for the angry-neutral (red) and happy-neutral (green) contrasts with the respective correlation maps with global performance scores (blue) revealed overlap in the right and left inferior frontal sulcus region (on the boundary between DLPFC and VLPFC) for the angry-neutral maps (left panel). Performance-correlated activity within these regions was not significantly (p = .49 right and p = .74 left) affected by the DTNBP1 genotype. For the happy-neutral maps, activity in right OFC did not overlap (right panel).

Supplemental material experimental chapter II

Tab.1 Main effect of group (RFX GLM): $p < .01$, cluster threshold 200 voxels

Location	R/L	x	y	z	Cluster size
LPFC	L	-27	19	26	320
LPFC	R	54	10	18	443
occipital-temporal cortex	L	-22	-74	-9	612
MPFC		2	18	43	270

Tab.2 Load 4-1 contrast (RFX GLM): $p < .05$, cluster threshold 500 voxels

Location	R/L	x	y	z	Cluster size
MPFC		2	16	49	4021
parietal cortex	R	27	-55	40	715
parietal cortex	L	-31	-58	45	1523

Tab.3 Interaction of emotion and group (RFX GLM): $p < .05$, cluster threshold 1500 voxels

Location	R/L	x	y	z	Cluster size
VLPFC	R	37	1	20	1760

Appendix A primary list of genetic variants

Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamate	Neuregulin 1	NRG1	8p12-p21	rs221132 /G rs221533 C rs241930 /G rs243177 / /T 433E1006 A/G rs3924999 rs2954041 SNP8NRG221533	0.12/0.88 0.30 0.34/0.66 / /0.33 0.15/0.85;		Modulation of glutamate activity (decrease) Regulation of neuronal development NRG1 elicit neuronal signal for cell proliferation and cell survival, synapically expressed, regulates activation and expression of neurotransmitter receptors, e.g. Regulates expression of NMDA and $GABA_A$ receptors	NRG1 knock-out mice severe abnormalities of neuronal development, abnormal behaviour and expression of less efficient NMDA receptors	Stefansson et al., 2002; p.a. Stefansson et al., 2003; p.a. Stefansson et al., 2004; Williams et al., 2003; p.a. Yang et al., 2003; p.a. Tang et al., 2004; p.a. Corvin et al., 2004; p.a. Li et al., 2004; p.a. Zhao et al., 2004; p.a. Iwata et al., 2004; n.a. Thiselton et al., 2004; n.a. Law et al., 2004; Kerber et al., 2003; Hashimoto et al., 2004; p.a. Falls DL. 2003; Liu et al., 2005;

									Buonanno and Fischbach, 2001; Murphy et al., 2002; Bao et al., 2003; Ozaki M. 2001; Crone and Lee, 2002; Roysommuti et al., 2003; Michailov et al., 2004
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamate	NMDA Receptor Subunit NR1 NMDA receptor subunit NR2B	GRIN1 GRIN2B	9q34.3 12p12	1719 G/A; IVS2-22 T/C; IVS2-11 G/A; IVS4-34 C/T; G1001C T4197C T5988C C366G G-200T (5'UTR) Rs1806201	0.97/0.03; 0.97/0.03; 0.97/0.03; 1.00/0.00	NR1 mRNA was lower and the level of NR2B mRNA higher in the hippocampus, superior temporal cortex of patients with schizophrenia (Gao XM et al., 2000; Grimwood et al., 1999) Expression of NR(1) and NR(2A) but not NR(2B)	Modulation of glutamate activity; transient NMDA receptor blockade in early development causes lasting cognitive deficits relevant to schizophrenia, significant genetic interaction between the G1001C in the GRIN1 gene and the T4197C and T5988C polymorphisms in the GRIN2B gene → suggest that the combined effects of the polymorphisms in the GRIN1 and GRIN2B	Mice with low NMDA receptor NR1 subunit behaviour neuroleptic drugs	Sakurai et al., 2000; p.a. Mohn et al., 1999; id.a. Miyamoto et al., 2001;id.a. Stefani and Moghaddam, 2005 id.a.; Qin et al., 2005 p.a.; Ohtsuki et al., 2001; p.a. Martucci et al., 2006 p.a. Di Maria et al., 2004 p.a.

						subunits was higher in the dorsolateral prefrontal cortex and the occipital cortex of patients with schizophrenia (Dracheva et al., 2001)	genes might be involved in the etiology of schizophrenia		
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamate	Metabotropic glutamate receptor 3	GRM3	7q21-22	Rs187993 T/G; Rs917071 C/T HCV11245618 A/G Rs1468412 A/T HCV2536213 G/A	0.68/0.32; 0.70/0.30; 0.73/0.27; 0.73/027; 0.75/0.25;	No significant effect	Predominantly presynaptic localization, Inhibits adenylate cyclase activity, postsynaptic GRM3 Ca^{2+}increase, implicated by the agonists glycine and PCP Affects hippocampal and PFC functions, Heteroreceptor modulating dopamine and serotonin transmission and associated effects, modulatory role, by contributing to fine-tuning of synaptic efficacy, and control of the accuracy and sharpness of the transmission		Egan et al., 2001; fMRI Fujii et al., 2003; p.a. Lewis et al., 2003; Cartmell and Schoepp, 2000; De Blasi et al., 2001; Spooren et al., 2003; Chen et al., 2005; p.a.

Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamate, Dopamine, GABA	Dysbindin	DTNBP1	6p22.3	rs760761 C/T rs909706 G/A rs1011313 C/T rs1018381 C/T rs1047631 G/A rs2005976 G/A rs2619522 A/C rs2619528 C/T rs2619538 A/T rs2619539 C/G rs2901727 T/C rs3213207 A/G rs15580740 A/G rs15643772 T/C rs2619538 T rs3213207 A rs1047631 A P1578	0.13/0.87	Reduced Dysbindin expression in schizophrenia, → confers risk, while high expression confers a protective effect Decrease of presynaptic dysbindin in hippocampus in schizophrenia; reduced mRNA and protein in DPFC, Differential expression of Dysbindin alleles suggesting cis-acting regulatory elements;	Modulation of glutamatergic transmission; Trafficking and tethering of NMDA, nicotinic, and $GABA_A$ receptors and signal transduction proteins, Expressed pre-and postsynaptically by many neuron populations, including pyramidal neurons in hippocampus and DPFC, substantia nigra and striatum Dysbindin might regulate the dopamine release of the dopaminergic system via modulation of SNAP25 expression. Down-regulation of dysbindin in cortex primary cultures resulted in reduction of SNAP25 expression and glutamatergic release. (rs2619528 & rs760761) were found associated with the NoGo-anteriorization (NGA) measured as an event-related potential	Sandy mouse with deletion mutation in DTNBP1 gene resulting in loss of dysbindin-1 protein (Li, W. et al., 2003)	Bray et al., 2005; p.a. Kirov et al., 2004; p.a. McClintock et al., 2003; p.a. (proteome) Schwab et al., 2003; p.a. van den Bogaert et al., 2003; p.a. Funke et al., 2004; p.a. Weickert et al., 2004; p.a. Talbot et al., 2004; p.a. Husi et al., 2000; Inoue and Okabe, 2003; Straub et al., 2002; p.a. Benson et al., 2001;

							elicited during the continuous performance test,		
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamate	D-Amino-Acid-Oxidase	DAAO G72 interacts with DAAO	12q24 13q34			Reduced D-serine levels in brain and blood of schizophrenics	Increased Oxidation of D-serine →decreased D-serine for allosteric activation of NMDA receptor		Chumakov et al., 2002 p.a. Kumashiro et al., 1995; Hashimoto et al., 2005 Schumacher et al., 2004 p.a.
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Glutamat	Proline-dehydrogenase	PRODH2	22q11	PRODH*1945 T/C			Proline-dehydrogenase involved in glutamate synthesis	PROHD-deficient mice → decreased PROHD activity, deficit in prepulse inhibition	Lui et al., 2002; p.a. Fan et al., 2003; n.a. Ohtsuki et al., 2004; n.a. Williams et al., 2003a, 2003b; n.a.

									Jacquet et al., 2002;
Amine and aminoacid neurotransmitter (e.g. glutamate, dopamine, GABA, serotonin)	Regulator-of-G-Protein-Signaling-4	RGS4	1q21-22	Rs159728879 A/G; Rs159729374 T/G; Rs159729723 G/A; Rs159735809 A/G Rs951439 C/T		Decrease of RGS4 gene transcription and translation in brain of schizophrenics	RGS-proteins decrease effects of G-protein-coupled receptor agonists by Increase of GTPase activity of G-protein-α-subunits → inactivation of G-proteins → shortens duration of G-protein-coupled synaptic signal transmission		Chowdari et al.,2002; p.a. Morris et al., 2004; p.a. Williams et al., 2004 p.a. Geurts et al., 2002;
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
Catecholamine neurotransmitter (e.g. dopamine, norepinephrine)	Catechol-O-Methyl-Transferase	COMT	22q11	Met/Val polymorphism Z26491 Rs737865 Rs165599	0.46/0.45±0.03	Val-haplotype of COMT reduced mRNA levels of COMT	COMT catabolize catecholamine neurotransmitters Dopaminergic neurotransmission altered in PFC and subcortical structures of schizophrenics, high COMT activity associated Val allele preferentially transmitted in schizophrenia,	COMT-deficient mice changes in catecholamine levels and behaviour	Shifman et al., 2002; p.a. Kunugi et al., 1997; p.a. Li et al., 1999, 2000; p.a. Chen X. et al., 2004; p.a. Bilder et al, 2003; DeMille et al., 2002;

							significant COMT genotype effect: Val/Val individuals lowest n-back performance, and Met/Met individuals highest performance		Palmatier et al., 1999; Glatt et al., 2003;p.a. Malhorta et al., 2002; Goldberg et al., 2003; Egan et al., 2001; fMRI Callicott et al., 2003; fMRI Bertolino et al., 2004; fMRI Ho et al, 2005; fMRI Smolka et al., 2005; fMRI Akil et al., 2003; p.a. Gogos et al., 1998; Huotari et al., 2002
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
dopamine	Dopamine receptor 1	DRD1 intronless	5q35.1	A-48G			D1 receptors high concentration in DPFC, G-protein coupled receptor, that stimulates Adenylate	Mutant mice exhibit locomotor hyperactivity, no response to	Xu et al., 1994; Sunahara et al., 1990; Lee F.J. et

							cyclase, DRD1modulates NMDA glutamate receptor-mediated functions through direct protein-protein interactions, Chronic blockade of dopamine D2 receptors, a common mechanism of action for antipsychotic drugs, downregulates D1 receptors in the prefrontal cortex and, produces severe impairments in working memory, these deficits were reversed in monkeys by short-term co-administration of a D1 agonist, regulate neuron growth and differentiation	DRD1 receptor agonists and antagonists	al., 2002; Castner S.A. et al., 2000; Kojima et al., 1999; n.a. Rybakowski et al., 2005 p.a. Abi-Dargham et al., 2002;
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
dopamine	Dopamine receptor 2	DRD2	11q22-23	Ser311/Cys; Val196Ala; Pro310Ser; A-241/G; insertion/deletion –141 of C	0.78/0.22	D2 receptor density, elevated in post-mortem brain putamen and caudate nucleus, even in tissues from neuroleptic-free or drug-naive patients	Alternations in dopamine transmission and dopamine receptors in schizophrenia, D2 receptors target of all antipsychotic drugs		Arinami et al., 1997; p.a. Ohara et al., 1998; p.a. Jonsson E.G. et al., 1999; Li T. et al., 1998; n.a. Breen G. et al., 1999; p.a. Seeman and

									Niznik, 1990; Glatt et al., 2003; p.a.
Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
dopamine	Dopamine receptor 3	DRD3	3q13.3	Ser9Gly/rs6280/ Bal I in exon 1			Activation of intracellular second messenger cascades, Significant effect on striatal habit learning		Crocq et al., 1992; p.a. Williams et al., 1998; p.a. Anney R.J. et al., 2002; n.a. Jönsson E.G. et al., 2003; p.a. Hellstrand et al., 2004; Szekeres et al., 2004; p.a. Keri et al., 2005; p.a.
dopamine	Dopamine transporter	DAT1	5p15.3	-48 A/G -67 A/T 40-bp VNTR			amine transporter, terminates the action of dopamine by its high affinity sodium-dependent reup-take into presynaptic terminals, integral membrane protein, PFC function e.g. WM	DAT knockout mice	Morón et al., 2002; Khodayari G. et al., 2004; p.a. Li T. et al., 1994; n.a.

Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
serotonin	Serotonin transporter	5-HTT	17q11.1-q12	5-HTTLPR allele s/ allele l	0.41/0.59	Altered transcription and expression of 5-HTT	via uptake of serotonin impact on serotonergic neurotransmission, changes in synaptic concentrations, impact on amygdala biology	Abnormal development of somatosensory projections in 5-HTT knockout mice	Lesch et al., 1996; Lesch and Mossner., 1998; Heinz et al., 2004; fMRI Ikeda M. et al., 2005; n.a. Dubertret C. et al., 2005; p.a. Hairi et al., 2002; fMRI
serotonin	Serotonin receptor 2A	HTA2A	13q14-q21	C102/T A-1438/G		Association between C allele and schizophrenia			Inayama et al., 1996; p.a. Williams et al., 1996, p.a. 1997; n.a. Spurlock et al., 1998; p.a. Abdolmaleky et al., 2004; n.a.
serotonin	Serotonin receptor 3A	HTR3A	11q23.1-23.2	C178T		Altered translation → altered expression of HTR3A, Less common T allele related to an increase of HTR3A expression	Expressed in amygdala, hippocampus, cingulate gyrus, 5-HT_3 receptor inhibits memory and learning in the amygdala and hippocampus through GABAergic inhibitory mechanism, modulator of neural activation in the human amygdala		Koyama et al., 2000; Staubli and Xu, 1995; Bloom and Morales, 1998; Turner T.J. et al., 2004; Niesler B. et al., 2001; n.a. Iidaka et al., 2005; p.a.

Related Transmitter System(s)	Protein	Gene(s)	Chromo-somal Local-isation	Poly-morphism(s)/ haplotypes	Frequency	mRNA and protein level	Assumed Functional Affect / relation to cognition/ schizophrenia	Animal Model(s)	References
GABA	Glutamic acid decarboxylase GAD_{67}	GAD1	2q31	HCV2177469 G/A; HCV2177469 T/C; HCV11637130 G/A; Rs872123 T/C HCV2177452 G/A Rs2270335 C/T Rs2241165 A/G HCV8823462 T/C HCV2177441 C/T HCV2177434 C/G Rs769390 A/C HCV8823482 C/T Rs3791850 G/A HCV8823522 A/G Rs872123 T HCV2177452 G Rs2270335 C Rs2241165	0.65/0.35 0.77/0.23 0.75.0.25 0.66/0.34 0.85/0.15 0.68/0.32 0.65/0.35 0.60/0.40 0.62/0.38 0.77/0.23 0.80/0.20 0.70/0.30 0.87/0.13 0.72/0.28 0.65	Decrease of mRNA level in neurons in DPFC in schizophrenics, Decreased GAD_{67} expression in PFC	Major GABA-synthesizing enzyme, Associations with Increased rate of frontal gray matter volume loss, eye-tracking deficits, childhood-onset of schizophrenia	Only heterozygous GAD67 Knockout mice survive that have ~ 1/3 reduction in GABA	Addington et al, 2005; p.a. Akbarian et al., 1995;

				A					

Abbreviations: p.a.- positive association; n.a.- negative association; w.a.- weak association and i.d.- indirect support for association; fMRI- genetic neuroimaging

Appendix B methodical details

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRIN1	Rs6293	ACAACAGCA TCCACCTGAG CTTCCTGCGC ACCGTGCCGC CCTACTCCCA CCAGTCCAGC GTGTGGTTTG AGATGATGCG TGTCTACAGC TGGAACCACA TCATCCTGCT GGTCAGCGAC GACCACGAGG GCCGGGCGGC TCAGAAACGC CTGGAGACGC TGCTGGAGGA GCGTGAGTCC AAGGCAGAGA AGGTGCTGCA GTTTGACCCA GGGACCAAGA ACGTGACGGC CCTGCTGATG GAGGCGAAAG AGCTGGAGGC CCGGGTCATC ATCCTTTCTG CCAGCGAGGA CGATGCTGCC ACTGTATACC GCGCAGCCGC GATGCTGAAC ATGACGGGCT CCGGTACGT GTGGCTGGTC GGCGAGCGCG AGATCTCGGG GAACGCCCTG CGCTACGCCC CA/GGACGGCAT CCTCGGGCTG CACCTCATCA ACGGCAAGAA CGAGTCGGCC CACATCAGCG ACGCCGTGGG CGTGGTGGCC CAGGCCGTGC ACGAGCTCCT CGAGAAGGAG AACATCACCG ACCCGCCGCG GGGCTGCGTG GGCAACACCA ACATCTGGAA GACCGGGCCG CTCTTCAAGA GAGTGCTGAT GTCTTCCAAG TATGCGGATG GGGTGACTGG TCGCGTGGAG TTCAATGAGG ATGGGGACCG GAAGTTCGCC AACTACAGCA TCATGAACCT GCAGAACCGC AAGCTGGTGC AAGTGGGCAT CTACAATGGC ACCCACGTCA TCCCTAATGA CAGGAAGATC ATCTGGCCAG GCGGAGAGAC AGAGAAGCCT CGAGGGTACC AGATGTCCAC CA	P/P	synonymous	G: 0.32	Multi-National

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRIN1	Rs1114 6020	Forward 5'-GTCCAGTTTCCAGGCTCTC-3' Reverse 5'-CTCCCCACAAGGTTCAGAAA-3' (Begni S. et al., 2003) Method: PCR amplification and digestion with restriction endonuclease BseRI	-	Untranslat ed (promotor region)	C: 0.09 in controls and 0.12-0.16 in schizophrenics (Begni S. et al, 2003; Rice S.R. et al., 2001)	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRIN2 B	Rs1806 201	Forward 5'-AGCGCCAGTCTGTAATGA-3' Reverse 5'-biotin-TTCACACCAGACAGGTTGC-3' Sequencing primer: 5'-AATGAACTCCCCCAC-3' (Tadic A. et al., 2005) and see also Alderborn et al., 2000 Method: PCR amplification and real time sequencing	T/T	synonymo us	A: 0.26 in controls	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRM3	Rs9170 71	Forward 5'- -3' Reverse 5'- -3' (Egan et al., 2004; Fujii et al., 2003; Fukumaki & Shibata, 2003; Norton N. et al., 2005)	-	untranslat ed	T: 0.27 in controls and 0.28 in schizophrenics (Norton et al., 2005)	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRM3	Rs1468412	Forward 5'- -3' Reverse 5'- -3' (Egan et al., 2004; Fujii et al., 2003; Fukumaki & Shibata, 2003; Chen Q. et al., 2005; Norton N. et al., 2005)	-	intron	T: 0.27 in controls (Norton et al, 2005) T: 0.17 in controls (Chen et al., 2005)	Caucasians East Asia

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GRM3	Rs6465084	Forward 5'- -3' Reverse 5'- -3' Method: TaqMan 5'-exonuclease allelic discrimination assay (Egan et al., 2004;)	-	intron	G: 0.27 in controls (Egan et al., 2004) G: 0.25 in controls and schizophrenics (Norton et al., 2005) Marenco S. Et al., 2006	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
NRG1	rs3924999	Forward 5'-ACTGGTTTCACACCGAAGGAC-3' Reverse 5'-CCAAGATGAGATCCATTTTCGC-3' (Yang J.Z. et al., 2003) Method: PCR-RFLP	Arg/Gln	nonsynonymous	G: 0.36 in schizophrenics (Yang et al, 2003) A: 0.49 in controls (Lin et al., 2005) A: 0.40 in controls (Hong et al, 2008)	East Asia Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
NRG1	Rs35753505	Forward 5'-GCATTAGAACTAGAACTTGCGTGA-3' Reverse 5'-TGGGAACTCTCCATCTCTTTCA-3' (Yang J.Z. et al., 2003) Method: dHPLC >SNP8NRG221533_AP201_LEN401_chr8 SNP= T/C AAATGCATTAGAACTAGAACTTGCGTGATTTTAAATT TTATTAGAAGTAGGTGTCAAGTTACCTAAGATGTCCA AGAGACAGCTGATGGGTTATGAGTTAAATTTTGGGTT CTGCTTATCATTTCTTAGAAATCAATTTAAGGCATCA GTTTTCAATAGCTTTTTTATGTATAACTAAAAAAGAG ATATATGATATTTGG T/C AAAATAAAGATACATGGCTTCCAGTCTCTTGAGACAT CTGTCTTCATGAAAGAGATGGAGAGTTCCCATTTCTA CTTACAAGAATGAATGTATGTCATAATAAAGACCAG CTATCATTTGTTATATACAAAATATGTGGTTCTTTCTT TGACTTTTTTTCTGGATTTAGACAACCACAGATGACA TTTATGAGAAATGAA (Stefansson et al., 2002)	A/G	nonsynonymous	C: 0.30 in controls and 0.38 in schizophrenics Stefansson et al., 2002) T: 0.33 in schizophrenics Yang J.Z. et al., 2003) T: 0.48 in controls and 0.46 in schizophrenics (Zhao X. et al., 2004)	Caucasians East Asia East Asia

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
NRG1	Rs?	1. Amplification Reaction Forward 5'-CCTACCCCTGCACCCCCAATAAATAAA-3' Reverse 5'-CTTCCTGTCGAGTGCCCCCTGCT- 3' 2. Amplification Reaction Forward 5'-TGCCACTACTGCTGCTGCT-3' Reverse 5'-ACCTTTCCCTCGATCACCAC- 3' (Stefansson et al., 2003) Method: Nested PCR SNP8NRG433E1006 allelePos=31 total len = 60 SNP= G/A chr8 GCGGCGGCCG GCAACGAGGC GGCTCCCGCG G/A GGGCCTCGGT GTGCTACTCG TCCCCGCCCA (Stefansson et al., 2002)	Arginine/Glycine	nonsynonymous	A: 0.15 in controls and 0.12 in schizophrenics (Stefansson et al., 2002) A: 0.12 in and controls 0.11 in schizophrenics (Stefansson et al., 2003)	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs2619 539	Forward 5'-AGTTTTTATCACTAATCAAAATGAAACAGCCTTT-3' Reverse 5'-CTCATTCTGTTATAACTAGTCTGACATGGT-3' Probe1 5'-VIC-TATTAGCTATGATAGTGTTTTAT-MGB-3' Probe2 5'-FAM-ATTAGCTATGATAGTCTTTTAT-MGB-3' (Numakawa T. et al., 2004) Method: TaqMan 5'-exonuclease allelic discrimination assay	-	intronic	C: 0.31 in controls and 0.32 in schizophrenics (Numakawa T. et al., 2004) G: 0.43 in schizophrenics (Kirov G. et al., 2004) G: 0.41 in controls (Fallgatter et al., 2006)	East Asia Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs3213 207	Forward 5'-GGAACTTTTCTTTGAAGACTTCCTTTCG-3' Reverse 5'-ACCACTAACAACCAAAAAGAAAACAAACA-3' Probe1 5'-VIC-TAAAGCCAATAATTACC-MGB-3' Probe2 5'-FAM-AGCCAGTAATTACC-MGB-3' (Numakawa T. et al., 2004) Method: TaqMan 5'-exonuclease allelic discrimination assay	-	intronic	G: 0.01 in controls and 0.03 in schizophrenics (Numakawa T. et al., 2004) G: 0.10 in schizophrenics (Kirov G. et al., 2004) G: 0.11 in controls (Fallgatter et al., 2006)	East Asia Caucasians
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs1011 313	Forward 5'-GATATGACTCCTTAATTCACAGGCTACAG-3' Reverse 5'-GTTACTGCACACAAGCAACTGTTAA- 3' Probe1 5'-VIC-AATGGATGTTGCATTAGT-MGB-3' Probe2 5'-FAM-ATGGATGTTGCGTTAGT-MGB-3' (Numakawa T. et al., 2004) Method: TaqMan 5'-exonuclease allelic discrimination assay	-	intronic	A: 0.15 in controls and 0.17 in schizophrenics (Numakawa T. et al., 2004) A: 0.08 in schizophrenics (Kirov G. et al., 2004) A: 0.08 in controls (Fallgatter et al., 2006)	East Asia Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs7607 61	Forward 5'-CCAATCCATTCTTTTATTGACATGGAGTTT-3' Reverse 5'-TGATTTTGACCAAGTCCATTGTGTCT- 3' Probe1 5'-VIC-AAAAGCACAAACAACAAG-MGB-3' Probe2 5'-FAM-AAAAGCACAAATAACAAG-MGB-3' (Numakawa T. et al., 2004) Method: TaqMan 5'-exonuclease allelic discrimination assay	-	intronic	T: 0.07 in controls and 0.10 in schizophrenics (Numakawa T. et al., 2004) Schwab et al., 2003 T: 0.20 in controls (Fallgatter et al., 2006)	East Asia Caucasians
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs2619 538 /Rs2619 528	Forward 5'-TCTGTTATGTGCCATTCACTGTTTT-3' Reverse 5'-TAGGGCTGGGATTGGATGA- 3' Probe1 5'-VIC-AGCAGTTTACTCTTGGG-MGB-3' Probe2 5'-FAM-AGCAGTTTACATCAGGG-MGB-3' (Numakawa T. et al., 2004) Method: TaqMan 5'-exonuclease allelic discrimination assay	-	intronic	A: 0.02 in controls and 0.04 in schizophrenics (Numakawa T. et al., 2004) A: 0.47 in schizophrenics (Kirov G. et al., 2004) Schwab et al., 2003 A: 0.20 in controls (Fallgatter et al., 2006)	East Asia Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DTNBP 1	Rs1047 631	Forward 5'-GTGGTGAGGACAGCGACTCT-3' Reverse 5'-GCTGTTCTTTAAGTTTCTCACACA-3' Extension primer 5'-TTCTCACACATTATTGGCAATTA-3' (Bray N.J. et al., 2005) Method: 'Hot Star' taq polymerase and genotyping by primer extension with SNAPshot Multiplex Kit	-	3'UTR	G: 0.13	Caucasians
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DAO	Rs3741 775	Forward 5'-AAAATTCAGCTTTAAAATCACTCC-3' Reverse 5'-AAAATTCAGCTTTAAAATCACTCT-3' 5'-TAGGATGTCAGACTTTATTCTAA-3' (Liu X. et al, 2004)	-	intronic	G: 0.34 in controls and 0.25 in schizophrenics (Liu X. et al, 2004) G: 0.49 in controls and 0.50 in schizophrenics (Chumakov et al, 2002)	East Asia Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
RGS4	Rs9514 36	Forward 5'-cagaagcctccctccttctt-3' Reverse 5'-tatacagcatcctccagccc-3' FP primer 5'-TCT TTG CTT TTT AGT CCT AAA A-3' (www.wpic.pitt.edu/research/schizgene/research/rgs4/data/index/html) Method: allele specific PCR	-	5'UTR (typically regulates gene expression)	T: 0.47 in controls and G: 0.49 in schizophrenics (Zhang F. et al., 2005) Williams et al., 2004 Morris et al. 2004 Prasad K.M. et al, 2005	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
RGS4	Rs9514 39	Forward 5'-agaaagaaagcttgggaggc-3' Reverse 5'-gttcacatcctgctgtgtgg-3' (www.wpic.pitt.edu/research/schizgene/research/rgs4/data/index/html) Method: allele specific PCR	-	5'UTR (typically regulates gene expression)	A: 0.38 in controls and 0.44 in schizophrenics (Zhang F. et al., 2005) Morris D.W. et al. 2004 Cordeiro Q. et al., 2005 Fallin et al., 2005 Prasad K.M. et al, 2005	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
RGS4	Rs2661319	Forward 5'-tggggcagagagataaggaa -3' Reverse 5'-aggtttggctccatcatcag-3' FP primer 5' CTC CAT CAT CAG AAA GGC ACT A 3' (www.wpic.pitt.edu/research/schizgene/research/rgs4/data/index/html) Method: allele specific PCR	-	intronic	A: 0.44 in controls and 0.48 in schizophrenics (Zhang F. et al., 2005) Williams et al., 2004 Cordeiro Q. et al., 2005 Prasad K.M. et al, 2005	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DRD1 Intron-less	D1.1 – 48 (5'UTR)	Forward 5'-ACTGACCCCTATTCCCTGCT-3' Reverse 5'-AGCACAGACCAGCGTGTTC-3' (Cichon S. et al., 1994) Method: PCR-RFLP, restriction enzyme DdeI		5'UTR	A: 0.11 in controls (Cichon et al., 1994)	Caucasians

Gene ID	Poly-mor-phism	Primer sequences or 200bp before and after polymorphism	AA Change	Type	Av. frequency minor allele	Pop.
DRD2	141C Ins Del	1. Dop2-Ex-Forward 5'-CTGGGTGGTGGGTGGGAGC-3' Dop2-Ex-Reverse 5'-TCGGCACTGAAGCTGGACAG-3' 2. Dop2-141c-Forward 5'-TTCCCGCCTCAAAACAAG-3' Dop2-141c-Reverse 5'-TGAAGCTGGACAGCTCTGC-3' (Jönsson E.G. et al., 1999) Method: Nested PCR Forward 5'-ACTGGCGAGCAGACGGTGAGGACCC-3' Reverse 5'-TGCGCGCGGTGAGGCTGCCGGTTCGG-3' (Arinami T. et al., 1997; Ohara K. et al., 1998; Li T. et al., 1998; Himei A. et al., 2002) Method: Amplification and RFLP on amplified fragments, digested with BstN1 Forward 5'-ACTGGCGAGCAGACGGTGAGGACCC-3' Reverse 5'-TGCGCGCGGTGAGGCTGCCGGTTCGG-3' (Arinami T. et al., 1997; Ohara K. et al., 1998; Li T. et al., 1998; Himei A. et al., 2002) Method: Amplification and RFLP on amplified fragments, digested with BstN1		Insertion/ Deletion in the promoter region	Del: 0.11 in controls and 0.06 in schizophrenics (Jönsson E.G. et al., 1999) Del: 0.10 in controls and 0.13 in schizophrenics (Li T. et al., 1998) Del: 0.180 in controls and 0.197 in schizophrenics (Himei A. et al., 2002) Del: 0.22 in controls and 0.14 in schizophrenics (Arinami T. et al., 1997) Del: 0.16 in controls and 0.10 in schizophrenics (Ohara et al., 1998)	Caucasian Caucasian East Asia East Asia East Asia

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
COMT	Rs4680	Forward 5'-CACCTGTGCTCACCTCTCCT-3' Reverse 5'-GGGTTTTCAGTGAACGTGGT-3' Extension primer 5'-CGGATGGTGGATTTCGCTGGC-3' (Smolka et al., 2005) Method: HotStar Taq-Polymerase or Forward 5'-TCGAGATCAACCCCGACTGT-3' Reverse 5'-AACGGGTCAGGCATGCA-3' 5'-6FAM-CCTTGTCCTTCACGCCAGCGA-3' 5'-VIC-ACCTTGTCCTTCATGCCAGCGAAAT-3' (Chen et al., 2004) Method: TaqMan 5'-exonuclease assay Forward 5'-CTCATCACCATCGAGATCAA-3' Reverse 5'-CCAGGTCTGACAACGGGT-3' (Galderisi S. et al., 2005) Method: based on Lachman H.M. et al., 1996, using 1.5 U Taq polymerase Forward 5'-GCCCGCCTGCTGTCACC-3' Reverse 5'-CTGAGGGGCCTGGTGATAGTG-3' (Han D.H. et al., 2004) Method: PCR-RFLP amplification and digestion by NlaIII enzyme	Val/Met	A/G nonsynoymous	G: 0.41 in controls and 0.46 in schizophrenics (Galderisi S. et al., 2005) G: 0.45 in controls (Egan et al., 2001) A: 0.47 in controls and 0.49 in schizophrenics (Daniels et al., 1996) A: 0.46 in controls (Norton et al., 2002) G: 0.27 in controls (Chen et al., 1999)	Caucasians Caucasians Caucasians Caucasians East Asia

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DRD3	Ser9Gly	Forward 5'-GCTCTATCTCCAACTCCTACA-3' Reverse 5'-AAGTCTACTCACCTCCAGGTA-3' (Lannfelt et al., 1992; Reynolds et al., 2005) Method: PCR-RFLP and digestion with restriction endonuclease MscI Forward 5'-GCTCTATCTCCAACTCCTACA-3' Reverse 5'-AAGTCTACTCACCTCCAGGTA-3' (Durany N. et al., 1996; Kéri S. et al., 2005) Method: PCR with 1.5 U Taq polymerase and digestion with 1 U MscI/15µl Forward 5'-GCTCTATCTCCAACTCTCACA-3' Reverse 5'-AAGTCTACTCACCTCCAGGTA-3' (Joober R. et al., 2000) Method: PCR with 1 U of Taq polymerase, amplified fragments digested with 2 U of Msc I	Ser/ Gly	Exonic A/G	Gly: 0.28 in controls and 0.30 in R schizophrenics and 0.37 in NR schizophrenics (Joober R. et al., 2000)	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
DAT1	40bp-VNTR 9 repeat / 10 repeat	Forward 5'-TGTGGTGTAGGGAACGGCCTGAG-3' Reverse 5'-CTTCCTGGAGGTCACGGCTCAAGG-3' (Joober R. et al., 2000) Method: PCR with 1 U of Taq polymerase Forward 5'-TGTGGTGTAGGGAACGGCCTGA-3' Reverse 5'-CTTCTTGGAGGTCACGGCTCAA-3' (Gelernter J. et al., 1998) Method: PCR amplification with PCR cycler and Taq polymerase, gentypes by size resolution of the alleles by gel electrophoresis of PCR product	No sequence change in DAT protein	40-bp repeat in 3' untrans-lated region of exon 15	9 repeat: 0.25 in controls and 0.26 in R schizophrenics and 0.30 in NR schizophrenics (Joober R. et al., 2000) 9 repeat: 0.27 in controls (Doucette-Stamm L.A. et al., 1995) 9 repeat: 0.22 in controls (Hemmings S.M.J et al., 2003)	Caucasians Caucasians Africans

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
SLC6A4 (5-HTT)	5-HTTLPR 44-bp insertion /deletion	Forward 5'-GGCGTTGCCGCTCTGAATGC-3' Reverse 5'-GAGGGACTGAGCTGGACAACCAC-3' (Malhotra A.K. et al., 1998; Serretti A. et al., 1999; Han D.H. et al., 2004) Method: PCR amplification 1 U of Taq DNA polymerase Forward 5'-GGCGTTGCCGCTCTGAATC-3' Reverse 5'-GAGGGACTGAGCTGGACAACCAC-3' (Collier D.A. et al., 1996) Forward 5'-GGCGTTGCCGTCTGAATGCC-3' Reverse 5'-CAGGGGAGATCCTGGGAGAGGT-3' (Stöber G. et al., 1998) Method: Standard PCR 0.5 U Taq DNA polymerase Forward 5'-ATGCCAGCACCTAACCCCTAATGT-3' Reverse 5'-GGACCGCAAGGTGGGCGGGA-3' (Gelernter J. et al., 1997) Method: PCR using KlenTaq polymerase Forward 5'-GGCGTTGCCGCTCTGAATGC-3' Reverse 5'-GAGGGGACTGAGCTGGACAACCAC-3' (Pae C.-U et al., 2005; Heils et al., 1996)		44-bp insertion/deletion in the 5' promoter region	short: 0.42 in controls and 0.43 in schizophrenics, (0.38 in paranoid subtype and 0.46 in non-paranoid) (Stöber et al., 1998) short: 0.34 in controls (Gallinat J. et al., 2005) long: 0.21 in controls and 0.18 in schizophrenics (Pae C.-U. et al., 2005) short: 0.37 in schizophrenics (Malhotra A.K. et al., 1998) short: 0.44 in controls and long: 0.46 in schizophrenics (Sanjuan J. et al. 2005)	Caucasians Caucasians East Asia Multinational Caucasians

Gene ID	Polymor-phism ID	Primer sequences or 200bp before and after polymorphism	AA Change	Type of polymor-phism	Av. frequency tri-allelic variant	Pop.
SLC6A 4 (5-HTT)	VNTR	Forward 5'-GCTGTGGACCTGGGCAATGT-3' Reverse 5'-GACTGAGACTGAAAAGACATAATC-3' (Bellivier F. et al., 2002) Method: PCR		17bp VNTR in intron2	12: 0.71 10: 0.28 9: 0.01 in controls (women) (Lauzurica N. et al., 2003) 12: 0.59 10: 0.40 9: 0.01 in controls (Ogilvie A.D. et al., 1996) 12: 0.54 10: 0.45 9: 0.01 in controls (Collier D.A. et al., 1996) 12: 0.54 10: 0.45 9: 0.01 in controls (Stöber et al., 1996)	Caucasians Caucasians Caucasians Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
HTR2A	C102/T	131 to 112 5'-TTAAATGCATCAGAAGTGTT-3' -61 to -42 5'-AGCAGAAACTATAACCTGTT-3' and 349 to 330 5'-CAAGTGACATCAGGAAATAG-3' 38 to 57 5'-CAACTACGAACTCCCTAATG-3' (Ishigaki T., 1996) Method: PCR with Taq Polymerase Forward 5'-TCTGCTACAAGTTCTGGCTT-3' Reverse 5'-CTGCAGCTTTTTCTCTAGGG-3' Method: PCR amplification (Warren J.T. et al., 1993; Arranz M.J. et al., 1997; Joober R. et al., 1999; Golimbet V.E. et al., 2002)	-	near the promoter region in exon1 position 102 T→C	T: 0.38 in controls (Hemmings S.M.J. et al., 2003) T: 0.43 in controls and 0.40 in schizophrenics C: 0.43 in controls and 0.41 in schizophrenics (Abdolmaleky H.M. et al., 2004) T: 0.40 in controls (Joober R. et al., 1999) C: 0.34 in controls and 0.33 in schizophrenics (Chen R.Y.L. et al., 2001)	Africans Caucasians East Asia Caucasians East Asia

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
5-HTR3A	A1596G	Forward 5'-CCATGGGAAACCACTGCAGCC-3' Reverse 5'-GCGTACTGCCAGATGGACC-3' Method: PCR for single-strand conformational polymorphism (SSCP), exon-specific primers (Niesler B. et al., 2001) Forward 5'-TGCTGGACAAGCTGCTATTC-3' Reverse 5'-CCAGATGGACCAGAGCATAAC-3' Sequencing primer 5'-AGGCCAGCACCGC-3' Method: Pyrosequencing (Nordfors L. et al., 2002)	-	In exon 9 A→G	G: 0.24 in controls and 0.18 in schizophrenics (Niesler B. et al., 2001)	Caucasians
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
5-HTR3A	C178/T	Forward 5'-TTTCCTCCCGCCTGAAAC-3' Reverse 5'-AAGTCCTGCTGCTTCCCG-3' Method: PCR-RFLP (Iidaka T. et al., 2005) Forward 5'-AGCTGGCCCTTGGTGGGCCCCG-3' Reverse 5'-CAGATGGTCAACCAAGTCC-3' Method: PCR, forward primer modified in its 3' end, creating 5' part of an AciI restriction site C/CCGC, 3' part of the restriction site is the more common C allele, cleavage of the 175-bp PCR product of the C alleles by the enzyme AciI (Melke J. et al., 2003) or Forward 5'-biotin-AGGCTGGCTGGGACATGAG-3' Reverse 5'-AGTGTGGGGAGGAGCAAGGC-3' Sequencing primer 5'-CCTCCGAGTGCTCAG-3' Pyrosequencing, PCR products generation with Hotstar Taq polymerase (Qiagen Inc); primer amplify a 151-bp product surrounding the C178T, detection of the SNP with reagent kit (PSQ 96 System; Pyrosesequencing AB) and sequencing primer (Nordfors L. et al., 2002)		5' UTR T→C	T: 0.20 in controls (Melke J. et al., 2003)	Caucasians

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GABBR1	Rs29218 A-7265G	Forward 5'- -3' Reverse 5'- -3' Method: ()		A→G in promoter region	G: 0.24 in controls and 0.17 in schizophrenics (Zai G. et al., 2005)	Multinational

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GABBR1	Rs29225 Ser-491-Ser-T1473C	Forward 5'- -3' Reverse 5'- -3' Method: PCR-RFLP ()	-	T→C at exon 12	C: 0.11 in controls and 0.16 in schizophrenics (Zai G. et al., 2005)	Multinational

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GAD1	Rs1978340		-	5'Flanking region	A: 0.25 in schizophrenics (Addington A.M. et al., 2005)	Multinational
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GAD1	Rs872123		-	5'Flanking region	C: 0.34 in schizophrenics (Addington A.M. et al., 2005)	Multinational
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GAD1	Rs3749034		-	5'UTR in exon 1	A: 0.15 in schizophrenics (Addington A.M. et al., 2005)	Multinational
Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GAD1	Rs2270335		-	In intron 1	T: 0.32 in schizophrenics (Addington A.M. et al., 2005) T: 0.25 in controls (Straub et al., 2007)	Multinational 90% Europeean American 10% Af. A.

Gene ID	SNP ID	Primer sequences or 200bp before and after polymorphism	AA Change	SNP type	Av. frequency minor allele	Pop.
GAD1	Rs22411 65		-	In intron 2	G: 0.35 in schizophrenics (Addington A.M. et al., 2005)	Multination al

Legend: Yellow – first selection
Orange – second selection
Green – confirmed (Listed)

Appendix C final list

Gene ID rs number	*Methodical details*					
	Forward primer	Reverse Primer	Annealing T in °C	Amplification fragment length in bp	Cutting enzyme	Cut genotype fragment lengths in bp
SLC6A4 5-HTT-LPR	5'-GGCGTTGCCGCTCTGAATGC-3'	5'-GAGGGACTGAGCTGGACAACCAC-3	61	SS=484 LL=528	/	/
NRG1 rs3924999	5'-AACTGGACTCCAACTTCTGAGG-3'	5'-ACACCGAAGGACTAGTTTGGAA–3'	60	**500**	Mfe I	**AA= 441bp+59bp GG=500bp**
DTNBP1 rs1047631	5'-GGTTTGGCTACAGTCAGCTCTT-3'	5'-AGGACAGCGACTCTTAAATTGG-3'	60	444	BsaA I	CC allele 121 and 321 TT allele 442 CT allele 121, 321 and 442
GRIN1 rs11146020	5'-TCAGTTGCTATTGGAAATGGTG-3'	5'-ATATTTCGGCTCCTGACTCTTG-3'	60	534	PshA I	CC allele 157 and 375 GG allele 532 GC allele 157, 375, 532
GRIN2B rs1806201	5'-TGGTGGTAGTGATCTTGGTACA-3'	5'-TTTGTGGTCATTTCTAGCCTCT-3'	58	422	Bts I	AA allele 118 and 302 GG allele 420 AG allele 118, 302, 420

Gene ID rs number	Methodical details					
	Forward primer	Reverse Primer	Annealing T in °C	Amplification fragment length in bp	Cutting enzyme	Cut genotype fragment lengths in bp
COMT rs4818	5'-CACCTGTGCTCACCTCTCCT-3'	5'- GGGTTTTCAGTGAACGTGGT -3'	60	348	Bcl I	CC allele 348 GG allele 159 and 189 CG allele 159, 189, 348
COMT rs4680	5'-CTCATCACCATCGAGATCAA-3'	5'-CCAGGTCTGACAACGGGTCA-3'	58	386	Nla III	GG allele 23 and 86 AA allele 18 and 68 GA allele 18, 23, 68, 86
RGS4 rs951439	5'-GGAAATTGTCATCTGAAGTGGT-3'	5'-TGGGAGGCAGAGTAAAAGAATA-3'	58	416	Bsr I	CC allele 43, 100, 272 TT allele 43 and 371 TC allele 43, 100, 272, 371
GAD1 rs2270335	5'-TCCGAGGGAGAACGTAAAGATA-3'	5'-GGAGAGACAAGAGGGAGGAAAG-3'	60	403	Bsr I	TT allele 96, 110 and 195 CC allele 32, 96, 110, 163 CT allele 32, 96, 110, 163, 195

Appendix D

Genetic variants	Genotype frequency	Allele frequency	Pearson Chi-Square and p-value (DF = 2)	
SLC6A4 5-HTT-LPR	LL = 21 LS = 24 SS = 11	ALL = 0.59 ASS = 0.41	0.47	.79
COMT rs4680	AA = 12 GA = 32 GG = 12	AAA = 0.50 AGG = 0.50	0.57	.75
COMT rs4818	CC = 16 CG = 32 GG = 8	ACC = 0.57 AGG = 0.43	0.76	.67
NRG1 rs3924999	GG = 22 AG = 28 AA = 6	AGG = 0.64 AAA = 0.36	0.17	.92
DTNBP1 rs1047631	CC = 0 CT = 13 TT = 43	ACC = 0.12 ATT = 0.88	1.04	.60
GRIN1 rs11146020	CC = 0 GC = 4 GG = 52	ACC = 0.04 AGG = 0.96	0.00	1.
GRIN2B rs1806201	AA = 5 AG = 25 GG = 26	AAA = 0.31 AGG = 0.69	0.04	.98
RGS4 rs951439	TT = 7 CT = 33 CC = 16	ATT = 0.42 ACC = 0.58	1.39	.50
GAD1 rs2270335	TT = 16 CT = 32 CC = 8	ATT = 0.57 ACC = 0.43	0.76	.67

OR are not applicable because genotype data is from control sample

Correlation between brain activity (beta difference) and WM performance (d'prime difference) for the difference between angry and happy faces

ROI	R^2	P (2-tailed)
left cingulate gyrus	0.00	.64
left frontal eye field	0.01	.49
right frontal eye field	0.00	.89
left frontal gyrus or SMA	0.00	.95
right inferior frontal gyrus	0.00	.94
right inferior frontal gyrus	0.01	.47
right middle frontal gyrus	0.00	.97
right middle frontal gyrus	0.00	.85
right occipital temporal junction	0.00	.66
right occipital temporal parietal ju.	0.01	.50
right STS	0.03	.19

ROIs based on the contrast angry-happy at $p < .05$ and clusterthreshold 200voxels

Appendix E

Screening questions for control participants:

Have you or any of your relatives ever consulted a clinical psychologist, psychiatrist or neurologist?

Did you or any of your relatives ever suffered from any mental illness, psychiatric or neurological condition, e.g. Schizophrenia, Bipolar Disorder, Depression, Alzheimer's Disease, Parkinson Disease, ADHD?

Have you suffered from a head injury?

Do you take any medication?

Did you have a surgery?

Do you have any implants?

Is it possible that you have any metal or magnetic objects in your body?

Did you ever work with metal (metal grinding)?

Are you claustrophobic?

Is it possible that you are pregnant or are you trying for a baby?

Details Patients

ID	Illness duration in years	Illness onset age in years	Dia-gnosis	Medication	Total PANSS score ICD10	Negative Factor	Positive Factor	General Factor	IQ NART premorbid
1	7.9	35.1	SA	20mg Olanzipine	62	16	16	30	106
2	1	17	PS	Perphenazine 6mg	76	18	18	40	118
3	4.9	18.1	PS	Clozapine 100mg aripiprazole 10mg	53	7	19	27	108
4	0.8	20.2	PS	4mg Risperidone	76	23	14	39	86
5	2.1	25.9	PS	Depot all 4 weeks 50mg/ml Pipotiazine	49	14	11	24	107
6	16.6	21.4	PS	800mg Amiloprid	45	9	15	21	116
7	5.3	21.7	PS	Clopixole depot 200mg	58	15	15	28	119
8	0.8	17.2	PS	Olanzapine 20mg	70	20	16	34	97
mean	4.9	22.1			61.1	15.3	15.5	30.4	107.1
SD	1.8	2.0			4.0	1.8	0.8	2.3	3.7