Application of functional near-infrared spectroscopy in psychiatry

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ABSTRACT

Two decades ago, the introduction of functional near-infrared spectroscopy (fNIRS) into the field of neuroscience created new opportunities for investigating neural processes within the human cerebral cortex. Since then, fNIRS has been increasingly used to conduct functional activation studies in different neupyschiatric disorders, most prominently schizophrenic illnesses, affective disorders and developmental syndromes, such as attention-deficit/hyperactivity disorder as well as normal and pathological aging. This review article provides a comprehensive overview of state of the art fNIRS research in psychiatry covering a wide range of applications, including studies on the phenomenological characterization of psychiatric disorders, descriptions of life-time developmental aspects, treatment effects, and genetic influences on neuroimaging data. Finally, methodological shortcomings as well as current research perspectives and promising future applications of fNIRS in psychiatry are discussed. We conclude that fNIRS is a valid addition to the range of neuroscientific methods available to assess neural mechanisms underlying neuropsychiatric disorders. Future research should particularly focus on expanding the presently used activation paradigms and cortical regions of interest, while additionally fostering technical and methodological advances particularly concerning the identification and removal of extracranial influences on fNIRS data as well as systematic artifact correction. Eventually, fNIRS might be a useful tool in practical psychiatric settings involving both diagnostics and the complementary treatment of psychological disorders using, for example, neurofeedback applications.

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Introduction

Two decades ago, the introduction of functional near-infrared spectroscopy (fNIRS) into the field of neuroscience created new opportunities for investigating not only healthy, but also abnormal functional processes within the human cerebral cortex. Starting with basic validation studies in the early and middle 1990s (e.g., Collier et al., 1995; Duncan et al., 1996; Hoshi and Tamura, 1993; Kato et al., 1993), fNIRS has been increasingly applied in psychological studies ever since, particularly focusing on visual (e.g., Herrmann et al., 2008a; Kato et al., 1993; Obrig et al., 2002), motor (e.g., Gratton et al., 1995; Hirth et al., 1996; Plichta et al., 2006), language (e.g., Herrmann et al., 2003; Quaresima et al., 2002; Watanabe et al., 1998), and cognitive paradigms (e.g., Herrmann et al., 2005; Hoshi and Tamura, 1997; Schroeter et al., 2002) in adult subjects, as well as perceptual and language tests in infants (e.g., Bartocci et al., 2000; Kotilahti et al., 2005; Kusaka et al., 2004; Zaramella et al., 2001).

Within the last decade, the scope of fNIRS research has been increasingly extended towards abnormal changes of cerebral hemodynamics during functional activation studies. To our knowledge, to date, at least 115 original research articles have employed fNIRS to investigate psychiatric research questions, ranging among over 900 research articles that applied fNIRS in brain activation studies in general (see Fig. 1). This development clearly emphasizes the increasing relevance of measuring cerebral hemodynamics in the human brain using fNIRS. Fig. 1 illustrates how the number of publications in the field of human brain research in general, as well as psychiatric neuroscience in particular, has increased especially within the past ten years.

Beside its versatile applicability, the methodological advancement of fNIRS strongly contributed to this trend. While early psychiatric neuroscience studies had to rely on relatively simple single- or four-channel systems (Fallgatter et al., 1997; Hock et al., 1997), the extension to multi-channel solutions up to the recent introduction of a 256-channel system (NIRx Medical Technologies LLC, Glen Head, NY) has allowed for the investigation of topographic research questions. Moreover, substantial progress has been made concerning data analysis (Abdelnour and Huppert, 2009; Angul et al., 2005; Cui et al., 2010; Plichta et al., 2007; Schroeter et al., 2004), artifact control and detection (Izzetoglu et al., 2005; Kang et al., 2009; Sato et al., 2006) and spatial registration of fNIRS data (Cutini et al., 2011; Singh et al., 2005; Tsuzuki et al., 2007, 2012).

Despite some remaining limitations (i.e., restricted depth and spatial resolution; confounding influence of extracranial signals and anatomical parameters; see discussion), fNIRS exhibits a number of important advantages making its application attractive for both neuroscience in general and psychiatric research in particular. First, the combinability of fNIRS with other brain imaging methods led to a strong increase in studies implementing simultaneous applications of fNIRS together with Doppler sonography (Hirth et al., 1997; Tachtsidis et al., 2008), fMRI (Heinzel et al., 2013a; Kennan et al., 2002; Lee et al., 2008; Strangman et al., 2002), EEG (e.g., Koch et al., 2008; Obrig et al., 2002), PET (Rostrup et al., 2002), and SPECT (Schi tz et al., 2009). Within the combination of different imaging modalities, fNIRS can thus strongly contribute to a holistic understanding of functional characteristics underlying neuropsychiatric illnesses. As another important advantage, fNIRS enables cortical hemodynamic assessments under circumstances where other methods fail (e.g., during real-life social interaction or whole body movements). Likewise, its easy applicability and high ecological validity make fNIRS particularly suitable for psychiatric patients who may be afraid of tight surroundings (e.g., in MRI/PET scanners) or show motor restlessness (e.g., in attention-deficit/ hyperactivity disorder [ADHD]) that interferes with motion-sensitive imaging methods such as MRI, EEG, MEG or PET. Taken together, the benefit of fNIRS in psychiatric research not only arises from its relative insensitivity to movement artifacts, but is further linked to its easy applicability and high versatility. Allowing for frequent measurement repetitions, fNIRS can be easily used for longitudinal studies that become more and more important for the investigation of the development and treatment of psychiatric disorders.

This review will provide a comprehensive overview of state of the art fNIRS research in psychiatry, particularly focusing on applications regarding the phenomenological characterization, treatment and etiology of psychiatric disorders as well as recent progress concerning diagnostics and classification (see Fig. 2). Published studies available in databases (PubMed, Google Scholar) before December 2012 were considered. Finally, research perspectives and promising future applications of fNIRS in psychiatry will be addressed.

Cortical alterations in psychiatric syndromes (Topic 1)

A large number of studies aimed at investigating differences between various groups of psychiatric patients and healthy control samples, in order to describe abnormal brain activity patterns potentially underlying the etiopathogenesis of a disease. In this respect, previous studies have mainly focused on schizophrenic (n = 20), affective (unipolar and bipolar depression; n = 15) and anxiety disorders (n = 9), as well as ADHD (n = 4), borderline personality disorder (n = 2), eating disorders (n = 2), and addiction (n = 1). Additionally, some analogue studies in healthy subjects were conducted to complement the clinical findings.

Schizophrenia and schizophreniform disorders (Topic 1a)

The first fNIRS study in schizophrenic patients was published in 1994, focusing on prefrontal laterality effects and interhemispheric integration during a mirror drawing task and using two one-channel fNIRS monitors (Okada et al., 1994). In this early work, data were analyzed mostly on a descriptive level by defining different types of “response patterns” and analyzing their relative frequency in controls and patients. As a main result, the authors detected an aberrant response pattern that was solely observed in schizophrenic patients (dysregulated pattern) which they interpreted in terms of a disrupted interhemispheric integration. In line with this finding, another early study confirmed an altered frontal laterization in schizophrenic patients during a Go–NoGo task (Fallgatter and Strik, 2000), a result that was also found in healthy subjects with high schizotypy scores during different cognitive tasks (Folley and Park, 2005; Hori et al., 2008a, 2008b). Since then, methodological advances have allowed for more systematic investigations of cortical function in schizophrenia using multi-channel fNIRS devices and/or more sophisticated data analysis strategies. Overall, these studies detected abnormal brain activation patterns in schizophrenias – particularly within the prefrontal cortex (PFC) – during various neurocognitive tasks (e.g., random number generation, Tower of Hanoi, Stroop, verbal fluency tests, Go/NoGo tasks) (e.g., Kubota et al., 2005; Quaresima et al., 2006, 2009; Shinba et al., 2004). In practically all cases, reduced hemodynamic responses were observed in prefrontal areas of schizophrenic patients compared to...
controls (e.g., Ehlis et al., 2007; Ikezawa et al., 2009; Quaresima et al., 2009; Shimodera et al., 2012; Shinba et al., 2004; Takeshi et al., 2010; Zhu et al., 2010)—even when samples were matched for performance differences (Watanabe and Kato, 2004) —thus replicating the general finding of cerebral hypofrontality also found by other neuroimaging methods (for a notable exception in a patient with resistant catatonic schizophrenia, see Grignon et al. (2008)). Using single-channel time-resolved spectroscopy (TRS) NIRS, Hoshi et al. (2006) extended the finding of cerebral hypofrontality to the resting state, for which reduced prefrontal hemoglobin concentrations were observed particularly in patients with a longer duration of illness (>10 years). Applying fMRI and fNIRS during the same working memory (WM) task in schizophrenic patients, Lee et al. (2008) showed a large concordance of fNIRS and fMRI findings, confirming the general validity of NIRS data also in clinical samples. By implementing more fine-grained analyses of the course of the hemodynamic response, Takizawa et al. found that frontal hemodynamics were slower to respond in schizophrenic patients during a verbal fluency task (VFT), with a steeper incline (slope) of oxygenated hemoglobin (O2Hb) concentration at the beginning of the task in healthy subjects (Takizawa et al., 2008). Additionally, prefrontal hemodynamic data were partly found to be impacted by clinical characteristics (i.e., age at onset; Koike et al., 2011a), medication effects (Watanabe and Kato, 2004), and psychopathological symptom scores (Ikezawa et al., 2009; Nishimura et al., 2011; Shinba et al., 2004) indicating a connection between PFC function and specific symptom dimensions. In an interesting attempt to differentiate individuals at different clinical stages of psychosis using fNIRS during VFT performance, Koike et al. (2011b) demonstrated that already subjects at ultra-high-risk for developing a psychotic disorder showed reduced activation within the ventro-lateral PFC as well as fronto-polar and anterior temporal regions as compared to healthy controls, while not differing significantly from patients in early (first-episode psychosis) or advanced clinical stages (chronic schizophrenia). In contrast, fNIRS activation within the dorsolateral prefrontal cortex (DLPFC) was highly sensitive to clinical progression, with an increasing decline in task-related O2Hb concentration across clinical stages (Koike et al., 2011b). Beyond these studies on different executive functions which consistently demonstrate the above-reported prefrontal deficits in schizophrenic patients, Platek et al. (2005) used fNIRS to study the impact of schizotypal personality traits on prefrontal hemodynamics during different tasks of self-other processing. They reported a differential association of schizotypy scores and prefrontal activation during self-face processing (negative correlation) vs. empathy (positive correlation). Similar approaches in clinical samples of schizophrenic patients are still lacking.

Affective syndromes (Topic 1b)

Regarding fNIRS research in affective disorders, the first study was again conducted by Okada et al. (1996) focusing on aspects of frontal lateralization in patients with major depression (MD) during a mirror drawing task. The main finding was an abnormal laterality pattern in about half the patients, with higher task-related activation in the non-dominant compared to the dominant hemisphere, which was never observed in healthy controls. Following this early work, frontal lobe abnormalities in depression were replicated in a number of fNIRS studies reporting decreased fronto-temporal oxygenation bilaterally in patients with unipolar depression using verbal fluency (Herrmann et al., 2004; Matsuo et al., 2002; Noda et al., 2012; Ohta et al., 2008; Pu et al., 2012a) and WM tasks (Pu et al., 2011; Schecklmann et al., 2011a). In some of these studies, fronto-temporal activation was found to be negatively correlated with symptom severity (Noda et al., 2012) and positively correlated with adaptive (task-oriented) coping (Pu et al., 2012a). Interestingly, studying healthy subjects during different affective states, Sato et al. (2011) found negative correlations between PFC activity and depressed mood during a verbal WM task. Similarly, in late-onset depression (LOD) task-related activation was found to be reduced in fronto-temporal areas during different cognitive tasks, and activation deficits —particularly within the fronto-polar cortex—were correlated with poor social functioning (Pu et al., 2008, 2012b). Reduced prefrontal oxygenation in LOD was also shown by Matsuo et al. (2005), even in the absence of performance differences. Furthermore, patients showed a reduced vasomotor reactivity in a CO2 inhalation challenge, indicating that a prefrontal microvascular dysregulation might underlie aspects of frontal lobe dysfunction in LOD.

Besides unipolar and late-onset depression, bipolar disorder has been investigated using fNIRS. Here, a reduced frontal lobe function could generally be confirmed during WM and VFT performance (e.g., Schecklmann et al., 2011a), even in remitted/euthymic stages of the disease (Matsuo et al., 2002, 2004, 2007). In contrast, Kubota et al. (2005) found a particularly strong prefrontal oxygenation in bipolar patients in tasks related to attention and non-verbal cognitive abilities, even in the presence of performance deficits. In a more complex temporal analysis, Kameyama et al. (2006) were able to differentiate unipolar from bipolar patients by their fronto-temporal activation patterns: While patients suffering from unipolar depression mainly showed a blunted O2Hb response in active task segments of a VFT, bipolar patients exhibited delayed O2Hb responses of normal amplitude. These findings indicate a potential advantage of the
relatively high time-resolution of fNIRS for the investigation of patients with different affective disorders which may offer new opportunities in diagnostics.

Anxiety and related diseases (Topic 1c)

NIRS studies on anxiety disorders have so far focused on panic disorder, post-traumatic stress disorder (PTSD) and dental phobia. For panic disorder, fNIRS studies indicate a reduced activation of particularly the left PFC during cognitive activation in general (Nishimura et al., 2007; see also Ohta et al., 2008 for findings of bilateral hypofrontality) as well as during confrontation with anxiety-relevant and other affective material (Akiyoshi et al., 2003) (for a case report on monozygotic twins discordant for panic disorder, see Tanii et al. (2010)). In a large sample of 109 panic patients, Nishimura et al. (2009) could furthermore show a significant correlation between task-related oxygenation changes and symptom severity, as left prefrontal O2Hb was negatively correlated with the frequency of panic attacks, whereas right prefrontal HHb was associated with the severity of agoraphobia. Right prefrontal activation was also enhanced in healthy subjects during anticipatory anxiety and correlated positively with harm avoidance (Morinaga et al., 2007).

For PTSD, previous findings indicate that – following a trauma – subtle differences in the hemodynamic response to trauma-related material might be able to differentiate between trauma victims with and without a subsequently developed PTSD (Matsuo et al., 2003a): While both groups showed increased prefrontal O2Hb concentrations during the presentation of trauma-related material, only PTSD patients additionally exhibited a significant decrease in HHb along with an enhanced skin conductance response. Moreover, PTSD patients showed significantly reduced PFC activation during a VFT, and this finding was related to deficits in attention and concentration (Matsuo et al., 2003b). Together, these studies indicate that PTSD patients show distinct alterations of cerebral hemodynamics when confronted with trauma-relevant material, whereas frontal dysfunction during cognitive tasks in general seems to be a corollary finding due to primary alterations in attentional capacity.

Finally, focusing on hemodynamic responses induced by auditory symptom provocation in patients with dental phobia, Koechel et al. (2011) reported an increased activation within the supplementary motor area (SMA) of female patients listening to the sound of a dental drill, possibly reflecting the priming of flight behavior during exposure. In a non-clinical sample, Kudo et al. (2008) found frontal cerebral blood flow to decrease during dentist-related sound material in subjects who had previously experienced unpleasant dental treatments. Due to the soundless nature of fNIRS measurements, the method is very well suited to examine cortical activation provoked by different (phobia-relevant) acoustic stimuli.

Personality disorders (Topic 1d)

Aiming at one of the most frequently investigated personality disorders, two fNIRS studies have so far investigated frontal lobe function related to emotion regulation (Ruocco et al., 2010a) and experiences of social exclusion (Ruocco et al., 2010b) in borderline personality disorder (BPD). When viewing sad picture material, BPD patients were found to exhibit a reduced slope of task-related O2Hb increases in left prefrontal channels as compared to controls (Ruocco et al., 2010a). Moreover, within BPD patients, a reduced O2Hb slope correlated negatively with clinical symptoms, i.e., ratings of interpersonal difficulties and abandonment fears, respectively. In contrast, during social exclusion experiences, BPD patients were found to show increased activation in the (medial) frontal-polar cortex (Ruocco et al., 2010b), suggesting different neural mechanisms to underlie different symptom dimensions. Further fNIRS studies on different types of personality disorders are so far lacking, however, there is some evidence that personality characteristics are related to frontal lobe hemodynamics as measured with fNIRS in healthy populations. Specifically, certain personality traits such as novelty seeking (Ito et al., 2005), agreeableness, and neuroticism (Sato et al., 2012) have been shown to correlate with cortical O2Hb changes. As personality reflects an important factor in psychiatric practice, future research should strive to further elucidate the exact relationships.

Eating disorders (Topic 1e)

To date, fNIRS studies investigating cortical patterns in patients with eating disorders are sparse. In a first, preliminary fNIRS study on cerebral oxygenation in eating disorders (EDs), Uehara et al. (2007) examined a mixed group of 11 patients with either anorexia nervosa or bulimia nervosa that was compared to a healthy control sample during VFT performance, and reported differences in task-related oxygenation for both fNIRS parameters (O2Hb, HHb). In a larger sample of 27 patients, Suda et al. (2010) found significantly reduced hemodynamic responses in patients with EDs within bilateral fronto-temporal regions. Moreover, dieting tendency and eating restriction/binge eating scores were correlated with task-related oxygenation in right fronto-temporal and left orbito-frontal regions, respectively, indicating a differential involvement of distinct cortical regions in different aspects of ED symptomatology. So far, fNIRS studies focusing on specific types of EDs are lacking.

Substance abuse (Topic 1f)

Finally, regarding fNIRS studies in addiction, Schecklmann et al. (2007) studied detoxified alcohol-dependent patients during a VFT, reporting overall reduced cerebral oxygenation in fronto-temporal areas despite regular task performance. While Hammers and Suhr (2010) confirmed a reduced PFC activation in polysubstance-using undergraduates, studies on the phenomenology of other substance-related or behavioral addictions are so far lacking.

fNIRS in the assessment of life-time brain function development (Topic 2)

About fifteen years ago, researchers started to use fNIRS to elucidate developmental aspects of cortical functions in psychiatric patients in order to complement pure phenomenological descriptions of altered brain activity. These studies include examinations at early stages of psychological anomalies in children, research on normal vs. pathological aging (e.g., Alzheimer’s disease), and studies investigating certain effects of age and aging-related diseases on specific brain functions.

Attention-deficit/hyperactivity disorder (ADHD) (Topic 2a)

Numerically, the majority of fNIRS studies on developmental disorders investigated children with ADHD. These studies particularly focussed on alterations in PFC activity during different experimental paradigms involving executive functions, such as Stroop tasks (Jourdan Moser et al., 2009; Negoro et al., 2010; Xiao et al., 2012), WM tasks (Schecklmann et al., 2010), the trail making test (Weber et al., 2005) or Go/NoGo paradigms (Inoue et al., 2012; Xiao et al., 2012). With the exception of one study, these investigations consistently point towards an attenuated oxygen metabolism within the frontal lobe, a dysfunction that is of particular interest in current treatment-oriented research concerning ADHD (see discussion). Recent fNIRS studies that investigated adult ADHD patients indicate that this hypofrontality seems to persist throughout development (Ehls et al., 2008; Schecklmann et al., 2008, 2011c, 2012).

Autism (Topic 2b)

Autism Spectrum Disorders (ASD) constitute another developmental pathology that has been frequently studied using fNIRS within
the past few years. Similar to ADHD, most of these surveys targeted prefrontal hemodynamics (Kawakubo et al., 2009; Kita et al., 2011; Tamura et al., 2012; Xiao et al., 2012), whereas others investigated effects of auditory stimulation on temporal areas (Funabiki et al., 2012; Minagawa-Kawai et al., 2009). While Minagawa-Kawai et al. (2009) demonstrated reduced left-lateralization during phonemic decoding in ASD patients, Funabiki et al. (2012) did not find abnormal activation patterns in the temporal cortex during auditory stimulation. However, they discovered reduced prefrontal hemodynamic responses in ASD children which were interpreted in terms of acoustic unawareness. Studies on ASD children are complemented by two articles dealing with pervasive developmental disorder (PDD) in adults, revealing reduced PFC activity during implicit processing of fearful facial expressions (Nakadoi et al., 2012) as well as verbal fluency (Kuwabara et al., 2006). Finally, in a mixed sample of ASD children and adults, Kawakubo et al. (2009) found bilateral PFC hypocapitation in ASD adults during the VFT, whereas this difference was not apparent in autistic compared to healthy children. Interestingly, healthy siblings of autistic adults showed a pattern of O2HB concentration changes that was intermediate between the one found in healthy controls and ASD subjects. In an innovative attempt to simulate real-life interaction, Suda et al. (2011) used fNIRS to study frontal-temporal activation in healthy adults during face-to-face conversations and found a negative impact of autistic traits even under relatively naturalistic conditions, which might be of particular relevance when studying cerebral correlates of social interaction, for example in autistic patients.

fNIRS in elderly subjects (Topic 2c)

Imaging of life-time brain development is not restricted to the examination of developmental disorders in children and young adults, but is also concerned with depicting neurophysiological functions in elderly individuals. A study conducted by our own group emphasizes the importance of age-related effects on cortical hemodynamics during cognitive tasks: Compared to young adults, elderly subjects showed diminished O2HB concentration increases and no left-lateralization of brain activation during a VFT (Herrmann et al., 2006). In a large sample of 325 healthy elderly subjects, we could further show that age predicted reduced cortical oxygenation within the inferior frontal junction as opposed to increased activity in the middle frontal and supramarginal gyri (Heinzel et al., 2013b) indicating compensatory processes or cortical reorganization.

Cerebral oxygenation in patients with Alzheimer’s Dementia (AD) was frequently investigated by means of verbal fluency tasks showing impaired hemispheric lateralization (Fallgatter et al., 1997) as well as reduced O2HB concentration increases (reflecting diminished cortical activation) within different brain regions, especially the DLPCF (Arai et al., 2006; Herrmann et al., 2008b) and parietal cortex (Arai et al., 2006; Hock et al., 1997). A lack of left prefrontal activation during a VFT was also found in elderly subjects suffering from MD (Matsuo et al., 2000), indicating that respective impairments may exist in different pathologies during aging. Only few studies have so far described reduced cortical activation in demented patients for cognitive domains other than verbal fluency, such as visuospatial orientation (Zeller et al., 2010) or arithmetics (Hock et al., 1996). Innovative attempts to investigate the effects of aging on cerebral hemodynamics have been made in studies comparing different subgroups of pathological developments – such as AD patients and patients with mild cognitive impairment (MCI) (Arai et al., 2006) – or by combining fNIRS with other hemodynamic methods, such as PET (Hock et al., 1997), Doppler Sonography (van Beek et al., 2010, 2012) or fMRI (Tak et al., 2011), in order to validate cortical anomalies observed in dementia. In the latter study, for instance, Tak and colleagues examined patients with subcortical vascular dementia (SVD) performing a simple hand grip task using 24-channel fNIRS and simultaneous fMRI in order to elucidate neurovascular coupling in this particular patient sample. As hypothesized, they found reduced cortical hemodynamic and metabolic responses in SVD patients within the motor cortex, and a decreased coupling of cerebral blood flow and the cerebral metabolic rate of oxygen. Beyond the opportunity of multimodal fNIRS utilization, Tomioka et al. (2009) presented another way to innovatively implement fNIRS measurements in AD research: Using a 52-channel ETG-4000 fNIRS system, frontal hemodynamic responses were assessed in AD patients and healthy controls while performing a) routine driving and b) a collision avoidance task in a driving simulator. AD was associated with lowered O2HB concentration increases during collision avoidance but not during low-risk routine driving. Interestingly, prefrontal oxygenation changes were positively correlated with breaking delays in healthy subjects, whereas AD patients showed a strong negative correlation, pointing towards a direct link between behavioural impairments and functional hemodynamic anomalies in AD. Together, these findings demonstrate the potential of fNIRS in assessing cortical oxygenation in developmental disorders, with particular advantages of the technique when studying children, low-health elderly subjects or cortical correlates of real-life functions.

Using fNIRS to investigate treatment effects (Topic 3)

Aiming at the investigation of pharmacological effects, fNIRS has been used to perform either psychiatric treatment studies or directly examine the effects of pharmacological agents on neural activation in experimental challenges.

Pharmacological effects (Topic 3a)

In the latter context, one study found decreased cortical oxygenation after heroine and methadone administration compared to saline intake in opioid dependent and healthy subjects in a resting state setting (Stohler et al., 1999). In contrast, Obata et al. (2003) reported no effects of acute alcohol intake on O2HB concentration changes in healthy subjects’ occipital cortex after visual stimulation. Beyond the investigation of acute pharmacologic effects, the easy applicability of fNIRS is particularly advantageous in longitudinal studies that require repeated measurements in a stable experimental setting. These studies are crucial for the examination of treatment effects following pharmacological, but also psychotherapeutic and neurophysiological interventions. Richter et al. (2007) were the first to use fNIRS to assess effects of galantamine on word fluency in patients with dementia over the course of four and eight weeks of treatment. Although brain activation within the DLPCF differed significantly between healthy elderly and patients, no treatment effect on brain oxygenation was observed. Furthermore, fNIRS studies have recently explored neurocognitive effects of methylphenidate (MPH) in ADHD children during attentional tasks and behavioral control paradigms (Monden et al., 2012; Weber et al., 2007). Schecklmann et al. (2011b) additionally examined adult ADHD patients and demonstrated attenuated fronto-temporal hemodynamic responses during olfactory stimulation in ADHD, whereby activation patterns within the temporal cortex tended to normalize under MPH medication, an effect potentially mediated by modulations within the dopaminergic system.

Non-pharmacological treatment (Topic 3b)

Beyond pharmaceutical treatment opportunities, several studies have focused on treatment effects of non-pharmacological interventions, such as neurostimulation techniques. In 2000, Eschweiler and colleagues started utilizing fNIRS to investigate clinical effects of repetitive transcranial magnetic stimulation (rTMS) applied over the left DLPCF in patients suffering from MD. In addition to significant symptom improvements
after active rTMS, these therapeutic effects were predicted by prefrontal hemodynamic responses during a mirror drawing task (Eschweiler et al., 2000). Moreover, Dresler et al. (2009) reported on an enhanced recruitment of prefrontal areas in a patient with panic disorder during panic-related task conditions following an add-on rTMS treatment. Finally, fNIRS has been applied before and after eye-movement desensitization and reprocessing (EMDR) in patients suffering from PTSD (Ohtani et al., 2009), animal-assisted psychotherapy for patients with affective disorders (Aoki et al., 2012), as well as in alcohol-dependent patients during different phases of withdrawal (Dresler et al., 2012), once again confirming the suitability of fNIRS for studying treatment effects in longitudinal as well as acute challenge settings.

**Imaging genetics (Topic 4)**

Etiologically, psychiatric disorders are strongly influenced by genetic factors with estimated heritabilities of up to 60% and more (e.g., Faraone and Doyle, 2000), while the influence of specific common alleles in such non-Mendelian polygenetic disorders is as expected quite low (e.g., International Schizophrenia Consortium et al., 2009). The “imaging genetics” approach aims at connecting the genetic level and the neural network domain with respect to the pathogenesis of mental disorders. Here, neural activity represents a dimensional intermediate phenotype (i.e., an endophenotype) that is assumed to be more tightly connected to the underlying genotype than the overtly diagnosed categorical phenotype (see Gottesman and Gould, 2003). Although the concept of endophenotypes with its varying definitions has been under debate throughout the last years and is being discussed in terms of multivariate genetic models (cf. Kendler and Neale, 2010), it has been proven to be a valuable tool in unraveling etiological factors of various mental disorders (e.g., Domschke and Dannowski, 2010).

With its potential to quickly assess large numbers of participants (easy application, few contraindications, fast setup), fNIRS is particularly suited to be used in imaging genetics studies. So far, it has mainly been applied in healthy populations (e.g., Hahn et al., 2011; Kopf et al., 2011a, 2011b; Tupak et al., 2013), while a few studies have also been conducted in psychiatric (particularly schizophrenic) patients. Takizawa et al. (2009b), who published one of the first studies in this field, could show that besides reduced prefrontal oxygenation in patients with schizophrenia, the catechol-O-methyl transferase (COMT) val158met polymorphism affected neural activation patterns: Within schizophrenic patients, the val/val homozygous group displayed significantly lower activation than patients carrying at least one met-allele, an effect that was not found in healthy controls, but could also be shown for patients with panic disorder (Tanii et al., 2009). As COMT is involved in prefrontal dopaminergic degeneration, with a much higher catalyzation rate in val-allele carriers, this finding indicates a genetic effect in patients with established alterations in dopaminergic transmission. According to the authors, these data fit the inverted u-shaped association of dopamine availability and prefrontal functioning (Tunbridge et al., 2006), with patients and controls being located on different positions on this function (Takizawa et al., 2009b). Takizawa et al. (2009a) could furthermore show an effect of the sigma-1 receptor (Sig-1R) gene, which modulates NMDA and dopamine receptor function, in schizophrenic patients. In a larger sample, this effect was also observed in controls (Ohi et al., 2011). Reif et al. (2011) employed two neurocognitive tasks in schizophrenic patients and found that a functional candidate gene for schizophrenia (i.e., NOS1) encoding nitric oxide (NO) – a second messenger of the NMDA receptor – influenced reaction times in the n-back task and prefrontal activation in the VFT only in patients. Here, the risk variant of the gene that has been repeatedly linked to schizophrenia (Reif et al., 2006) resulted in prolonged reaction times and reduced prefrontal activation. In ADHD patients that were administered MPH in a cross-over design, Oner et al. (2011) found that PFC activation during a Stroop task was dependent on two polymorphisms within the syntaposomal associated protein 25 (SNAP-25), indicating interesting interactions between specific SNAP-25 genotypes and MPH-induced neural effects.

Taken together, these data show that fNIRS is suited for imaging genetics studies and can contribute to findings on genetic variants putatively involved in altered dopaminergic and glutamatergic neurotransmission underlying the pathophysiology of, e.g., schizophrenia.

**Discussion**

In this review, we present the range of fNIRS applications in psychiatric settings that relate to different major research questions (i.e. phenomenology, life-time development, treatment effects and genetic influences). Currently, the number of available studies illustrates the huge potential of the technique in psychiatric contexts, while also allowing us to assess previous shortcomings and deduce potential future applications and improvements in experimental designs as well as data analysis strategies.

So far, most fNIRS studies in psychiatric settings have been conducted on prefrontal activation and the phenomenology of psychological disorders, with the VFT being the most popular paradigm (Dieler et al., 2012). In the beginning, using only few channels and to avoid artifacts caused by dark hair, the measurement of prefrontal regions represented a good starting point for fNIRS research, but given more recent technical developments (e.g., multi-channel systems) these approaches should be expanded to include alternative cortical regions, especially since neuropsychiatric disorders are mostly based on alterations in distributed cerebral networks. Furthermore, although the VFT as a simple paradigm has been proven to reliably show differences between patients and controls, it only covers a restricted aspect of neurocognitive functions (i.e., executive functioning) while being relatively unspecific, which might partly explain why related cortical activation seems to be altered relatively independent of the specific diagnosis (see 2.1). In future fNIRS research, activation paradigms should be chosen that are more specifically tailored to the study population of interest, thereby increasing the chance of detecting etiologically relevant alterations with improved diagnostic specificity (see Fig. 3 for an example of fNIRS data in schizophrenic patients vs. controls elicited by the presentation of literal and metaphorical sentences; Schneider et al., unpublished data). In light of recent efforts to develop individually tailored therapeutic strategies for psychiatric illnesses, a more specific assessment of clinically relevant cortical alterations would constitute an important step along this way.

Against this background, future studies should also focus on the usefulness of fNIRS as a supportive tool for choosing the most promising treatment approach for a specific patient. Using fNIRS, neurophysiological markers that might predict treatment outcomes (and may thus be relevant for personalized medicine) could be easily identified. Whereas studies using EEG or fMRI have already reported on various biomarkers associated with different psychiatric diseases that may contribute to therapeutic outcome prediction (e.g., Ehlis et al., 2012; Wagner et al., 2010), so far only one fNIRS study has investigated the predictive significance of prefrontal activation patterns for therapeutic efficacy in patients with major depression (Eschweiler et al., 2000). The authors could show that reduced DLPCF activation together with a good performance during mental work predicted therapeutic rTMS effects. Future fNIRS studies could pick up on this finding also with respect to other psychiatric disorders and the wide range of treatment options.

Besides the investigation of neurophysiological predictors for treatment responsiveness, fNIRS has recently been started to be implemented as a treatment tool itself, particularly in terms of neurofeedback interventions. While first results on real-time NIRS-neurofeedback during motor imagery have already been published (Mihara et al., 2012), our
own laboratory currently assesses the effectiveness of a prefrontal fNIRS feedback training in adult ADHD patients in a prospective, randomized, controlled treatment study, after first training data in healthy subjects revealed some promising results (Ehlis et al., in preparation). If positive therapeutic effects of neurofeedback trainings using fNIRS can be confirmed, such interventions could offer alternative or additional treatment options in neuropsychiatric syndromes such as ADHD, anxiety disorders or depression.

Moreover, while fNIRS has been extensively used to phenomenologically describe alterations in cerebral oxygenation in various groups of psychiatric patients, its potential within the diagnostic process has been far less explored. In 2004, Suto et al. (2004) reported that patients with depression and schizophrenia seemed to show disorder-specific fNIRS patterns and suggested that fNIRS could provide a useful option for clinical purposes in psychiatry. In the last few years, more sophisticated approaches (e.g., discriminant analyses; pattern classification using multiple biomarkers) have been proposed and initial studies for schizophrenia are available (Azechi et al., 2010; Hahn et al., 2012). Using such approaches, the correct assignment to the respective classes was about 75%, which indicates that they might actually offer additional diagnostic information and could aid the diagnostic process, especially in combination with non-neural markers and prior probability information. Based on such findings, the Japanese health ministry already confirmed fNIRS as an “advanced medical technology” and approved its use “in limited facilities to assist differential diagnosis of depressive state as a clinical trial for evaluation of its clinical usefulness (the Advanced Medical Technology Program)” (after Cyranoski, 2011). While we agree that this might be a valuable option in the future, we feel that more fNIRS research is needed to identify valid markers of neuropsychiatric illnesses with increased diagnostic specificity, before fNIRS can improve the diagnostic process in psychiatric disorders.

Despite rapid methodological advances, one of the factors that currently still hamper the use of fNIRS in practical psychiatric scenarios concerns technical and methodological difficulties that may complicate the interpretation of fNIRS data in psychological studies, particularly in clinical populations. Beside its limited depth resolution (e.g., McCormick et al., 1992; Wabnitz et al., 2010) that prevents an assessment of subcortical areas which often play a major role in neuropsychiatric disorders (e.g., the amygdala in anxiety disorders), the reliability of fNIRS data has been shown to be affected by anatomical parameters, such as scalp-to-cortex distance (SCD; Cui et al., 2011; Haeussinger et al., 2011) and peripheral hemodynamic parameters (i.e., skin perfusion; Kirilina et al., 2012; Takahashi et al., 2011; Tong et al., 2011). These factors could be potential confounding variables, especially in clinical samples that might exhibit increased SCD (e.g., in case of cortical atrophy in patients with AD, schizophrenia or anorexia nervosa) or enhanced peripheral perfusion due to heightened emotional or stress responses under certain task conditions (e.g., while processing affective or trauma-related material in affective disorders or PTSD). Moreover, in light of the ongoing development of new systems and the recent and current increase in fNIRS applications, there is a strong need for empirically based, uniform, and user-friendly analysis strategies that would improve comparability between the wide range of studies and support the development of clear-cut neuropsychiatric markers. Although commonly accepted approaches (concerning, e.g., data filtering, motion artifact removal or spatial registration) exist (e.g., Cui et al., 2010), standardized guidelines for fNIRS data analyses are still lacking.

In summary, we conclude that fNIRS is a valid addition to brain imaging methods assessing neural mechanisms underlying neuropsychiatric disorders. While the technique has clearly already shown its potential in the phenomenological description of altered brain activation patterns in various psychopathological syndromes, future...


Conflict of interest statement

The authors declare that they have no actual or potential conflicts of interest associated with this work.

References


