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In Pursuit of Non-Invasive Psychopharmacology: Developing fNIRS Repertoire

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Abstract

The need for objective physical criteria in psychiatric diagnosis has greatly increased the use of imaging and electrical recording that can monitor brain activity. Functional Magnetic Resonance Imaging (fMRI) has assumed a dominant role in evaluation due to its relatively high spatial resolution; however, supporting technologies are increasingly important adjuncts that offer important confirmatory determinations. Among these Functional Near Infrared Imaging Spectroscopy (fNIRS) has proved valuable for its ability to monitor brain activity in mobile patients, the capacity to measure both oxygenated deoxygenated forms of hemoglobin, and relatively low cost. Due to current technological and biological constraints the technique's theoretical potential for improved spatial resolution and compositional analysis remains latent, however, which potentially could exceed that of fMRI in functional analysis. A cluster of new experimental methods for improving light delivery and sampling suggest that prospects for developing this latent ability and for assessing functional connectivity and psychopharmacological variables is likely to be positive.

Introduction

Clinical assessment constitutes the current gold standard for psychiatric evaluation. Yet the wide use of diagnostic modalities that can directly monitor brain activity also reveals a desire for more objective clinical standards [1]. Among the various factors invoked to explain cognitive disease, for example, are flawed circuit connectivity, local trauma, developmental errors, and the like, which are not directly revealed by clinical evaluation. Detection technologies therefore function to confirm clinical assessment by identifying disease related differences in brain activity, with an overall view toward discerning etiopathology [2,3]. The emphasis on brain activity changes has thus placed technologies capable of high sensitivity and high spatial and temporal resolution as the chief diagnostic tools for psychiatric evaluation, including functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG), and Magnetoencephalography (MEG). Of these, early theses of cognition on the focal siting of cognitive functions favored the technology with the best spatial resolution. Accordingly, fMRI has since assumed a dominant role in evaluation because of its high spatial resolution relative to that of electrical recording techniques like EEG and MEG, which excel at temporal resolution.

fMRI is a specialized application of MRI, employing a unique sequencing of radio frequency pulses that have been developed to assess brain activity. The application draws from Pauling and Coryell's 1936 observation that oxygenated and deoxygenated hemoglobin possess magnetically distinguishable properties, whereby oxygenated hemoglobin is repelled and deoxygenated hemoglobin attracted by the presence of a magnetic field. Ogawa's extrapolation [4] of this observation to activity dependent oxygen consumption, subsequently led to the technology's preeminence for measuring neural activity by relating it to changes in hemoglobin oxygenation. Specifically, focal depletion of oxygenated hemoglobin in capillaries close to neurons leads to a local surge in its replacement, which can be assessed by fMRI. Due to the link between neural activity and oxygen consumption Ogawa's Blood Oxygen Level Dependent (BOLD) response has therefore been applied to measure neural activity in very localized zones of neural tissue. fMRI's ability to discriminate activity differences between small regions has thus been linked both to the spatial resolution of the technique itself and also to localized blood responses arising from capillary flow. Nonetheless, despite the combination of these influences, an overall optimum of about 1 mm to 3 mm can be achieved, considerably better than even high, multichannel EEG recordings. On the other hand, fMRI is limited in a number of other respects [5]. The speed of the BOLD response, which is only

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about 1 to 2 seconds, means that the response is nearly three orders of magnitude slower than individual activity events that are being measured; hence, fMRI is capable of only summing overall activity occurring within a region of interest. Additional factors include low signal to noise ratios that require statistical processing, maintaining of patients in immobile and otherwise abnormal postures, equipment expense, and an advancing understanding of cognition that has tended to favor more global associations in functional activity. Spurious sources of activity contributing to background variation are multiple. Of these, cognitive activity, which is continuous, generates ongoing background 'noise' that is exacerbated by generalized variations in local blood flow needing baseline adjustment. MRI and fMRI also require sophisticated and relatively massive technologies. High magnetic fields for molecular stimulation necessitate weighty magnetic field generating and recording equipment, where signal acquisition is differentially processed. Due to confined settings and measuring restrictions on bodily motion, further, experimental design is limited. Additionally, instrumentation units capable of 1.5 tesla fields can exceed two million dollars, limiting access to the technology only in large institutional settings. Finally, cognition itself is undergoing a paradigm shift, from the originally widely held view of focally confined, functional activity to the current view that effective connectivity is globally distributed; hence, interpretations of acquired data have also changed.

In response to these limitations new efforts at technological development have attempted to leverage the strengths of fMRI, while overcoming its most obvious drawbacks-those of poor temporal resolution, lack of equipment versatility, and expense-with complementary technologies [6,7]. For example, fMRI has been used in conjunction with EEG recording, particularly with electrical markers like the local field potential, to link the observed fMRI activity to real time electrical events. Of these technologies, there is growing interest in near infrared spectroscopy to monitor brain related events [8,9]. In its current stage of development Functional Near Infrared Spectroscopy (fNIRS) offers several significant advantages over fMRI for monitoring brain activity including a) the ability to monitor the hemodynamic response in mobile patients, b) the monitoring of both states of hemoglobin oxygenation, as opposed to only one in fMRI, c) portability, and d) low cost. Whereas, for example, new formats have substantially increased in expense, from 10s of thousands of dollars for continuous wave configurations to 100s of thousands for frequency and time domain configurations, costs of even the most expensive fNIRS units pale relative to that of fMRI units, which can exceed 20 fold or greater fNIRS unit expense. In consequence, growing interest in the technology has propelled the appearance of numerous research publications exploring its capabilities [9]. From a low of 5 articles per year in 1995, published research exceeded 130 articles per year in 2015, a roughly 25 fold increase in publication rate and a confirmation of future interest in expanding the technology's use for study of functional brain activity. Despite its chief use for measuring the hemodynamic response, however, the technology fundamentally differs in its principle of operation from that of fMRI [10]. Specifically, the technology monitors infrared absorption properties, as opposed to the magnetic moments detected in fMRI; accordingly, its analytical scope is both distinct from fMRI and expected to resemble its parent technology, NIRS. Hence, it offers unrealized strengths that are not available with fMRI.

On the other hand, despite fNIRS significant advantages and the increasing scope of use, a number of shortcomings converge to restrict its further evolution. Among the chief limiting factors are a) low spatial resolution, which is more than a magnitude less than fMRI, b) low temporal resolution, which while comparable to fMRI, is nonetheless several orders of magnitude slower than the neural events that are the object of study, and c) light path obstructions affecting light travel and depth, and absorption from dominant absorbers like hemoglobin and water. These shortcomings have been mitigated somewhat in practice by combining fNIRS with other technologies, such as Electroencephalographic (EEG) recording, that complement deficiencies of fNIRS with improved capabilities in other dimensions. Nonetheless, fNIRS possesses considerably less discrimination power than NIRS when used forin situ or in vitro applications. Improving fNIRS capability for spatially resolving activity domains of interest, for example, or its ability to detect compounds influencing or involved with interneuronal communication would be of significant benefit for psychiatric clinical diagnosis.

Accordingly, it is of interest to determine whether fNIRS can overcome its current performance limitations, not solely to obtain a low cost and experimentally enhanced version of fMRI but as a tool specifically providing near infrared information. This capability would broaden the data acquisition repertoire associated with brain activity, and potentially expand the diagnostic range of psychiatric evaluation.

fNIRS-Replicating fMRI's Imaging of the Hemodynamic Response

Both fNIRS and fMRI represent imaging techniques that are specialized applications of more general parent analytical methods, which are purposed to assessing neural activity indirectly in terms of activity dependent oxygen consumption, that is, the BOLD or hemodynamic response. Because the principles of detection of each parent technology differ, there is some question of whether the two methods measure oxygen consumption equivalently. This question is significant since indirect or unrelated variables affecting measurements of total activity presumably differ as a function of the modality; in principle, these could significantly distort assessments of oxygen consumption depending on the method chosen. Current evidence, in fact, indicates that neither method measures neurovascular coupling alone. In the case of fMRI, signal intensity is related to several hemodynamic factors including regional blood flow and blood volume, which are linked to metabolic rate [11]. A direct relation between the hemodynamic response, cerebral blood flow and the Blood Oxygen Level Dependent (BOLD) response is thus not mathematically equivalent. The BOLD response, for example, has been shown to vary according to stimulus type. For fNIRS, measurements of oxidation dependent absorption have the potential for including other absorbing sources, such as cytochrome oxidase, which potentially influence absorption readings. More significant, absorption determinations depend upon light path length, which is an unknown in fNIRS and needs to be approximated. Despite these uncertainties dual use studies of the techniques have generally indicated a good correlation between measurements obtained by either method [12], which has been taken as indicating general concordance.

On the other hand, fNIRS is incapable of spatial resolution better than 1 cm to 3 cm in diameter, which is roughly 10 fold less than the current capability of fMRI [8]. Although this resolution permits the assessment of regional activity variation, the considerable overlap of functionally linked activity levels within a domain of such large size

limits functional interpretation vis-a-vis fMRI. fMRI is therefore a preferred medium where patient mobility is not a confound. The chief theoretical obstacle to spatial resolution in NIRS where light travel is unimpeded, however, is optical diffraction. This means that due to the direct relationship between diffraction and wavelength, probing stimuli using infrared radiation are in principle capable of a spatial resolution of several um. This limit, nearly four orders of magnitude better than that obtained with fNIRS, approximates the size of many smaller neurons and even axonal processes and is revealing of the great hindrance to spatial discrimination encountered in fNIRS. On the other hand it is indicative of the considerable capability that lies latent in the technology and that could accrue through improvements in spatial resolution.

By contrast, the spatial resolution of fMRI is limited, not chiefly on theoretical grounds, but due to practical features that relate to the length of time required for sampling. The need to conduct independent raster sampling in order to variably phase encode emitted resonance signals means, in particular, that the total time of measurement is a function of the number of raster's selected [13]. In principle, overcoming existing hindrances in the methods thus opens the possibility not only to improving fNIRS current spatial resolution but even to exceeding that of fMRI.

Overcoming *in vivo* obstacles to improved spatial resolution

Among chief obstacles that have limited the spatial resolution of fNRIS are light path obstructions and travel, and photon scattering [8,10]. Light travel through the cranium and brain tissue assumes a complex profile that is curved in shape and which is defined by the sensitivity of the source detector pair. Its depth, moreover, is relatively shallow and limited to the superficial cortex. Given the high probability for scattering, path travel is mathematically described by radiative transport, which can be simplified to a diffusion equation. Shallow depth penetration and light dispersion thus account for current limitations to fNIRS analysis that then assumes radiative travel features. Overcoming these hindrances, accordingly and unlike fMRI, relates primarily to the technical issues of light delivery and detection, difficulties shared in multiple imaging disciplines. Several methods have evolved to overcome these limitations in the physical analysis of thick tissue specimens and whole tissue cross sections. Among the techniques holding especial promise for expanding the compositional scope and localization potential of NIRS in functional brain imaging are optical sectioning of thick tissues with laser imaging microscopy and whole body photoacoustic tomography, briefly discussed in the following. A third approach that has been widely adopted for research settings is two and multi-photon laser scanning of thick tissue slices. However, the latter's depth of penetration is less than the other two methods and has been the subject of a number of reviews; accordingly it will not be discussed here.

Thin sheet laser imaging. In thin sheet laser imaging optical sectioning projects a thin light sheet through a sample to illuminate a plane of tissue and then sections the tissue into a series of consecutive planes. Observation is orthogonal to the tissue plane and to date has been configured with a system of lenses typically used for microscopy and adapted for small animal specimens. Originally conceived as early as 1903 [14] using ordinary light the technique now relies exclusively on synchronized radiation of laser light sources [15]. Spatial resolution approaches the diffraction limit below 10 um. However, the quality of light depends on the geometry of the light sheet, which outside of the focal plane assumes a Gaussian shape; accordingly, observations need to be made in the focal plane to avoid image distortion. The technique has been used for small animal brain tissue, such as rat and zebrafish; for example, stacks of 20 um serial sections of zebrafish brain have been compiled with spatial resolution approaching the diffraction limit.

Photoacoustic computed tomography: Images of even larger samples that include the significant impediment of crania, and lens configurations that are optimized for planar samples, have been obtained using whole body, ring shaped configurations that employ confocal photoacoustic computed tomography. In photoacoustic tomography laser illumination generates focal, small temperature increases in tissue, which induces thermoelastic expansion in the region of illumination [16,17]. The resulting pressure wave can be detected by ultrasonic transducers and the temporally displaced signals reconstructed to form the tissue image. In the ring configuration, light delivery occurs across a 360 degree profile that is focused through a conical lens and optically condensed to project a probing band around the sampling region. Photoacoustic signals can then be detected with a full ring transducer array spanning 360 degrees. Reported values for spatial resolution with this system approach 100 um. The system offers a depth of penetration that significantly exceeds current use with single light sourcing and multichannel detection, as well as an established detection technology. Significantly, illumination can be tuned to directly monitor spectral features deep within tissue.

Functional Imaging Using NIRS in Psychiatric Analysis

Taken together, the prospect of significantly improving spatial resolution in fNIRS suggests that functional interpretations of brain activity for psychiatric analysis can also be greatly improved in interpretive power. However, to date use of fNIRS in psychiatric study has limited investigation only to demonstrating observable differences between healthy controls and individuals with clinically identified symptoms or to validating fMRI findings, study limitations that likely relate to the technology's inferior spatial resolution ability. For example, in an fMRI study directed to characterizing neural correlates of explicit emotion recognition in schizophrenia [18] emotion impairments were linked to activity dependent dysfunctions in a wide number of affective loci, including the affective locus of the anterior cingulate cortex, bilateral dorsomedial prefrontal cortex, right superior temporal and the right fusiform gyri. A corresponding study with fNIRS that cited the fMRI research [19] obtained similar findings but were less well resolved, only linking hypoactivation to the right precentral and inferior frontal areas; that is, it offered confirmatory but less precise determination. Low spatial resolution is a significant restriction on the scope of fNIRS applications since acquired data are correlative and imply a limited degree of causal influence; that is, the activity parameter is, in practice, correlated with the phenomenon of interest, which is understood to be a direct or indirect outcome of the monitored activity. In consequence, reducing spatial discrimination reduces interpretive power with regard to identifying causal associations within a spatially defined matrix.

Due to the complexity of the variables intervening between or in association with two correlated processes, in fact, neither fNIRS nor fMRI data reflect strict indicators of causal precedence. In consequence, experimental paradigms seek increasingly to refine and narrow inferred connectivity relationships. Aided by greater power in spatial discrimination, experimental paradigms can thus in principle

diminish the uncertainty of causal inferencing. Indeed, in the case of fMRI a number of new paradigms and data treatment methods have been developed [1,18] that can significantly improve confidence in the temporal precedence and effective connectivity of activity relations. On the other hand, given the inferior spatial resolution of fNIRS, such paradigms have not been employed with this method.

Increasingly, these paradigms confirm that functionally related activity is distributed over broad neural ranges, often globally. For psychiatric disease experimental paradigms therefore now seek to monitor intrinsic activity relations between widely separated regions or attempt to detect differences arising from globally induced activity, usually in response to task based paradigms. Graph theoretic network analysis obtained from fMRI data of schizophrenia patients of the first rank, for example, has revealed a loss of module structure in these patients [19]. In the case of fMRI a number of such paradigms have been developed [20,21] varying from simple demonstrations of task correlated activity to complex dependency relations, where activity in one zone is 'causally' linked to activity in one or multiple other brain regions. The general linear model that is frequently used in diagnostic settings, for example, presumes that the observed activity changes are related to multiple independent variables, where the recorded pixel value is equivalent to the linear combination of explanatory variables plus a Gaussian error term. Other well known task based paradigms include Psycho Physiological Interaction (PPI), Dynamic Causal Model (DCM), Granger causal model, and multivoxel pattern analysis. The dynamic causal model, for example, is an approach to estimate effective connectivity and the influence on connectivity of different experimental variables. The procedure involves the building of a reasonably realistic model of interacting brain regions and then supplementing how this model would be transformed by the influencing variables in task based circumstances. In the Grainger causality model, by contrast, estimates of connection directionality assume that causal influences possess temporal precedence. Data analysis therefore search for time shifted versions of activity patterning among different brain regions. To date similar data treatments have not been used with fNIRS, reflecting the general difficulty in drawing causal conclusions in the absence of better spatial discrimination. Due to the general consonance between fMRI and fNIRS, nonetheless, relatively modest improvements in spatial resolution can be expected to provide sufficient discrimination to implement these methodological approaches, and improvements that exceed the spatial resolution of fMRI can be expected to yield wholly new paradigms.

fNIRS and Psychopharmacology: Extending Functional Monitoring Through Compositional Analysis

Psychiatric diagnosis and therapy is also intimately associated with chemical neurotransmission, as evidenced by the numerous pharmaceutical products affecting the metabolism and delivery of neurotransmitters at multiple stages [22]. These stages involve processes both within and without cells that include such features as intracellular messaging, e.g., Ca and cGMP, and intercellular neuronal communication involving neurotransmitter release, persistence, and receptor binding. Unlike fMRI, infrared detection has the intrinsic ability to identify an exceptionally broad group of chemical compounds; the use of fNIRS to monitor these components, therefore, has the significant potential to identify candidates and assess processes directly associated with clinical symptoms. Accordingly, improvements in *in vivo* compositional analysis and the imaging of compounds are likely to offer greater interpretability to diagnosis by dissecting out factors contributing to aberrant brain activity.

The technique's potential for compositional analysis derives from the great number of compounds that absorb chiefly in the near infrared region of the electromagnetic spectrum [23,24], from about 700 nanometer to 2,500 nanometers. Absorbances in this spectral range are due to quantum mechanical vibration modes of the principal carbonyl and common hydrogen bonding elements found in cells, that is, NH, OH, and SH moieties. These can be detected in both absorption and scattering modes. Within the longer wavelength range, from about 1100 mm to 2,500 nm, absorption is due to fundamental and largely asymmetric combinations of vibration modes, whereas absorption of shorter wavelengths below this range includes many vibrational overtones, absorption coefficients of which are 10 or more fold less. The asymmetry of chemical group combinations generates wide variance in absorbances and so yields unique spectra for a large number of compounds. Vibrational combinations may also be probed with intermolecular interactions, such as, for example, electronegativity of neighboring atoms or mechanical coupling with other vibrational modes, which introduce additional frequency shifts. Some vibrations, moreover, are sited to particular chemical groups and provide characteristic narrow frequencies despite the remaining complexity of the molecule. By comparing these with empirical tables they can be relatively easily detected and identified. Nonetheless due to spectral overlap, the relatively lower absorptivity in the near infrared region, and the complexity of some physical matrices, NIRS data obtained from *ex vivo* sampling typically require mathematical processing of accumulated data to isolate and quantify signal contribution [25,12]. Affecting component identification especially is tissue complexity, which is complicated with contributions from dominant IR absorbers. Indeed, one consequence of the material complexity of tissue is the favoring of detection of dominant absorbers in tissue with unfiltered spectra. As a result data treatment must either account for overlapping spectra of tissue constituents or be capable of number reduction. Significantly, besides mathematical treatment, number reduction can also be achieved physically by techniques capable of spatially isolating small tissue zones [26]. Dominant absorbers of infrared radiation in the brain include hemoglobin in its oxygenated and deoxygenated forms and water. While the chief absorption of hemoglobin is in the visible range, there is also substantial absorption occurring between 750 nm and 850 nm for both states [8]. Absorption spectra of oxygenated and deoxygenated hemoglobin states, being known, are amenable to subtractive filtering, a process that can further enhance signal detection. Water absorbs strongly in the infrared region, generally above 900 nm, but there is considerable variation as a function of wavelength that is related to the lesser extinction of vibrational overtones in the near infrared, and the relatively discrete localization of absorbance to particular wavelengths that is related to the simplicity of water's molecular structure. Water, significantly, possesses only three fundamental vibrations. Peak maxima lie in the far infrared at 2898 nm, 2,766 nm, and 6,097 nm. In the near infrared peak absorbance occurs at 970 nm, 1,200 nm, 1,450 nm and 1,950 nm. For the latter, absorption intensities are comprised chiefly of the fundamental vibrational overtones, and so are considerably weaker than fundamental vibrations. The absorption band at 698 nm, for example, that gives water its light blue tint, is a third vibrational overtone. Regions between near-infrared bands can and have been used for aqueous solute analysis, i.e., for absorption of

solutes dissolved in water [27,28]; hence the contribution of water to IR absorbance does not exclude the monitoring of other compounds. Indeed, while water absorbance is a significant contaminant affecting compositional analysis, it is not insurmountable, as evidenced in scans of tissue specimens (below).

In complex mixture analyses NIRS has been used as an imaging tool to probe solid mixtures, where its ability to detect spectral absorption of compounds in either transmittance or scattering modes enables the discrimination, localization, and identification of compounds in complex samples. That is, despite the presence of dominant absorbers, the use of the parent method has already available a wide range of component reduction techniques. Pharmaceutical preparations, for instance, can be modified to detect minute sample quantities with high spatial resolution by capturing the reflectance spectra with microscopic optics and focusing these on two dimensional detection arrays. In these configurations, data collection is comprised of spectral recordings taken from individual point sources over the near and mid infrared spectrum. From compiled data three dimensional data sets, termed hypercubes, are generated, which include x and y coordinates of the surface points and a z coordinate constituted from the spectral information. NIRS imaging thus enables direct quantitative information to be taken from the heterogeneous samples [23]. Using this approach it is also possible to detect and quantify the spatial distribution of unique compounds across the surface of an analyzed sample; hence, it is capable of detecting and locating compounds that would otherwise be hidden in transmission modalities directed through the sample.

Significantly for *in vivo* analysis, NIRS has been used to examine biological samples taken from prepared tissue specimens and neuronal cultures. The ability of the technique to assay minute regions, of a dimension much less than that used in fNIRS, reveal that limitations to spatial resolution are not intrinsically related to theoretical principles of its application and can effectively achieve number reduction by reducing the volume of examined material. For example, Lasch and Naumann [25-30] have used NIRS for frozen slide preparations of colon mucosa to assess both compound discrimination and spatial resolution; that is, with the inclusion of the dominant absorbers of water and hemoglobin. With this approach they were able to achieve a spatial resolution of 8 microns. Examination of colonocytes within the mucosa revealed the presence and characteristic IR signature of mucin glycoprotein. Furthermore, with Fourier transform deconvolution spatial contrast signal to noise ratios were further amplified. In a frozen neurological sample of dorsal root ganglia infected with scrapie virus, disaggregates of the prion protein were differentiated at spatial resolutions of 10 um. The spectral signature of the amide I/II band-a distinctive marker for proteins with abundant beta sheet structure-was detected at 0.1% background protein levels, indicating the capability of resolving even minute components. Finally, in a technically comparable study, the progression of amyloidogenesis was also monitored with NIRS [31] with the demonstration of plaque presence in diseased tissue. Together these studies suggest that with suitable technical isolation NIRS can identify and quantify components relevant to psychiatric diagnosis.

Ca and Neurotransmitters

Among the most significant psychopharmacological compounds are Ca ion and neurotransmitters. Ca2+, notably, is released intracellularly with the arrival of the action potential at synaptic termini before mediating the detachment of synaptic vesicles from their mooring and the release of their neurotransmitter contents into the synaptic cleft. Because the cell maintains a tight control on intracellelular concentration levels-only 1/10,000th that of the extracellular medium-release of Ca from intracellular stores strongly contrasts with background and so is relatively easily detected. Numerous CA probes, capable of detecting and signaling synaptic activity, are now available and a number have been developed with sensitivity in the IR range [32]. This has enabled access to deeper neural tissues due to the greater travel distance of IR light, by tuning the stimulating light; moreover, absorption can be tailored to the spectrum of the probe. Significantly absorption generates a local thermal increase that can be monitored photoacoustically [17] due to the transmissibility of the sonic wave through the tissue; hence it is also possible to detect probe specific information related to CA release by detecting thermoelastic expansion induced by absorbing CA probes.

Among the inherent difficulties in probe imaging is tissue access. However, difficulties in delivery of CA probes to neural tissue are also being overcome with a number of vehicles capable of delivery to brain tissue, including both natural and artificial vectors. Recent progress in the engineering of viral delivery vehicles and synthetic nanoparticles, for instance, now provide for several routes to site brain based probes. Foust et al. [33], for example, reported that AAV serotype 9 (AAV9) was able to traverse the blood brain barrier, and yield widespread transgene expression in both astrocytic and neuronal cells. The list of viral vectors used for therapy is extensive, and their potential is further amplified by a variety of genetic engineering procedures that can modify discrete bases or large modular sequences [34]. In contrast to viral vectors, on the other hand, non-viral, nanoparticles lack cell targeted biomolecular modalities. However, they are potentially amenable to a much broader range of synthetic alterations, making them, in many instances, a preferred mode of transport. Nanoparticles not only can be made from a variety of molecular compounds but also be constructed from numerous nanometer sized configurations, including liposomes, nanotubes, and magnetic nanoparticles [35].

Neurotransmitters: Monitoring the distribution and concentrations of various neurotransmitters is particularly significant for diagnostic psychopharmacology. To date earlier procedures for monitoring neurotransmitters by iontophoresis have been plagued by slow response times. Now, however, many new combinations of nanomaterials with polymers and biomolecules are being developed that have the potential for neurotransmitter sensing. Among the more promising are probes containing precious metals, like gold, silver, and palladium [36,37]. While such probes have generally been used to measure electrical differences, new probes are also being developed that are sensitive to electromagnetic radiation.

Conclusion

Although fMRI has assumed a dominant role in providing objective assessments for psychiatric evaluation fNIRS is increasingly important for independent and confirmatory determinations. Clear differences between the specialized technique of fNIRS for detecting functional, brain activity and that of its parent method of NIRS raise the obvious question of whether such theoretical capability is exploitable, that is, whether the greater analytical capability of the latter can be appropriated to improve diagnostic interpretation and provide an IR specific reservoir of information. Despite significant impediments due to material complexity and light travel obstruction,

the development of applications for focal illumination and IR tunable, transmissible sonic media hold promise for significantly improved assessment of functional connectivities and psychopharmacological determinations.

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