STATE OF MICHIGAN

IN THE

SUPREME COURT

ON APPEAL FROM THE MICHIGAN COURT OF APPEALS
SHAPIRO, P.J., AND BORRELLO AND, O'BRIEN J.J.

PEOPLE OF THE STATE OF MICHIGAN,

Plaintiff-Appellee,

-vs-

MONTARIO TAYLOR,

Defendant-Appellant.
_____/

Supreme Court No. 166428

Court of Appeals No. 349544

Circuit Court No. 16-040564-FC

APPENDIX TO PLAINTIFF-APPELLEE'S

SUPPLEMENTAL BRIEF ON APPEAL

Katie R. Jory (P78698)
Senior Assistant Prosecuting Attorney

Counsel for Plaintiff-Appellee

900 S. Saginaw Street
Flint, Michigan 48502
(810) 257-3210
kjory@geneseecountymi.gov

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STATE OF MICHIGAN

IN THE 7TH CIRCUIT COURT (COUNTY OF GENESEE)

PEOPLE OF THE STATE OF MICHIGAN,

vs Case No. 16-40564-FC

MONTARIO MARQUISE TAYLOR,

Defendant.
_____/

SENTENCE

BEFORE THE HONORABLE RICHARD B. YUILLE, CIRCUIT JUDGE

FLINT, MICHIGAN - MONDAY, FEBRUARY 25, 2019

APPEARANCES:

For the People: JENNIFER CASS JANETSKY P62808
Assistant Prosecuting Attorney
900 South Saginaw Street
Flint, Michigan 48502

For the Defendant: JESSICA R. MAINPRIZE-HAJEK P70942
Attorney at Law
503 S. Saginaw Street, Suite 519
Flint, Michigan 48502
(810) 767-7383

Recorded by: Via Video Recorder

Transcribed by: Shelie Robinson CER 6913
Certified Electronic Recorder
(810) 424-4454

additions to be made?

MS. MAINPRIZE-HAJEK: Yes, Judge. You were kind enough to adjourn this from February 11. So we would ask for today's date for the sentencing date and then that would entitle my client to an additional two weeks of jail credit. So 14 days. I believe that would be 852 days of jail credit.

THE COURT: It would be. Any other corrections or additions?

MS. MAINPRIZE-HAJEK: No, Your Honor.

THE COURT: Mr. Taylor, did you read the report as well? Did you go through that report?

THE DEFENDANT: Yes, sir.

THE COURT: Do you have any other corrections or additions to be made?

THE DEFENDANT: No, sir.

THE COURT: Ms. Janetsky, anyone here who wishes to address the Court?

MS. JANETSKY: Yes, Your Honor. The family is present, as they have been all of the time for both trials, and I believe Andre is going to address the Court.

THE COURT: Come up, sir. Good afternoon. Tell me your name.

MR. WILEY: Andre Wiley.

THE COURT: What is it you want to say, sir?

MR. WILEY: I just want to ask him why? Why did you do that to him?

THE DEFENDANT: I never (inaudible).

MR. WILEY: That was my little brother and he was loved by everybody.

THE DEFENDANT: I understand, but I didn't do it.

THE COURT: It's not going to do any good to proceed on that level so.

MR. WILEY: I don't got nothing to say now.

THE COURT: All right. Wait a minute. One more person wishes to speak? Tell me your name, ma'am.

KENISHA: Kenisha.

THE COURT: And you are?

KENISHA: His niece.

THE COURT: And what is it that you would like to say?

KENISHA: I first want to let you know that this is -- because of you, this is our first murder for our family. No one ever been murdered and our family before. Because of you, my uncle would never be able to meet his kids, his baby. He have an autistic son that he will never be able to meet again

because of you.

I mean you took our family -- you ripped a hole in our family because of you. Murder, like we never endured this before, never. And I see your smirks and all that. I can tell it really don't matter to you no more. It really don't. But it matter to us because my children love Montel. We love Montel. Montel never hurt a fly. Never.

I mean, if it was family, yeah, we all got into it, but Montel never had any -- as much hate as I guess you have to kill him. I just want to let you know that you are very wrong. You are wrong. And I had -- like before coming here, I had -- I'm kinda shook up and my words might not be coming out right. Before coming here today, I had -- I prayed, I prayed that you get this time.

When I left here the day that you got convicted, I really felt sorry for you. I really did. And I don't wish this on nobody.

But what you did to our family is horrible, horrible. My uncle will never come back. Your family can talk to you. You have a son, I know that, and you are going to talk to your son. He have three kids that he will never talk to and that's because of you.

So I just want you to think about what you

did to my family. You killed someone. No one in my family have ever been shot to death. No one.

THE COURT: Thank you. Ms. Janetsky, anything you want to say before I impose sentence?

MS. JANETSKY: Your Honor, I will just very briefly just say this was a trial that we did twice. You are very familiar with the facts of the case. This was a senseless act of violence. There was no reason on God's earth for him to walk into that house and shoot Montel dead. If there was any dispute between them at all, at all, it was over something very, very small, a little bit of cocaine or a little bit of marijuana. There was nothing going on that would have required him to lose his life in such a violent fashion.

He died alone in his house on the floor of his home underneath the photograph of his family. It was an awful killing. It was a vicious slaying and there is no leniency with respect to sentence. So there's no point in me belaboring it. He is going to go to prison and he is going to stay there forever and that's what should happen in a case like this where a senseless murder took place.

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about.

You know, I found it interesting that I think the one person who was there left to go confirm with the family how he should respond to what he just saw and that was interesting to me. I think I understand it from the racial sense that, over the years, African-Americans perhaps don't trust white police officers and white individuals. Maybe that's the reason. He wanted to go down and see what the family thought he should do before he did it and then he did it.

You sat right there throughout the whole trial, did make a sound, didn't -- your expression never changed and I don't know how anyone so young can be so hardened as you were during this trial. You just -- it just -- it's like it wasn't you.

And I know you are standing there saying you didn't do it but that's the first time I heard it right today. I didn't hear you say it any other time. So I'm not buying the fact that you are not guilty of this charge. Actually, it doesn't matter how I view it anyway. The jury made the decision and the jury convicted you of first degree premeditated murder.

I have no options as to the sentence. I do feel bad about sending someone your age to prison for

REVIEWS

What we can do and what we cannot do with fMRI

Nikos K. Logothetis[1]

Functional magnetic resonance imaging (fMRI) is currently the mainstay of neuroimaging in cognitive neuroscience. Advances in scanner technology, image acquisition protocols, experimental design, and analysis methods promise to push forward fMRI from mere cartography to the true study of brain organization. However, fundamental questions concerning the interpretation of fMRI data abound, as the conclusions drawn often ignore the actual limitations of the methodology. Here I give an overview of the current state of fMRI, and draw on neuroimaging and physiological data to present the current understanding of the haemodynamic signals and the constraints they impose on neuroimaging data interpretation.

Magnetic resonance imaging (MRI) is the most important imaging advance since the introduction of X-rays by Conrad Röntgen in 1895. Since its introduction in the clinic in the 1980s, it has assumed a role of unparalleled importance in diagnostic medicine and more recently in basic research. In medicine, MRI is primarily used to produce structural images of organs, including the central nervous system, but it can also provide information on the physico-chemical state of tissues, their vascularization, and perfusion. Although all of these capacities have long been widely appreciated, it was the emergence of functional MRI (fMRI)—a technique for measuring haemodynamic changes after enhanced neural activity—in the early 1990s that had a real impact on basic cognitive neuroscience research. A recent database (ISI/Web of Science) query using the keywords 'fMRI' or 'functional MRI' or 'functional magnetic resonance imaging' returned over 19,000 peer-reviewed articles. Given that the first fMRI study without exogenous contrast agents was published in 1991, this corresponds to approximately 1,100 papers per year, or over 3 papers per day. This average obscures the actual rate of publications, as in 1992 there were four publications in total, increasing to about eight per day by 2007. About 43% of papers explore functional localization and/or cognitive anatomy associated with some cognitive task or stimulus—constructing statistical parametric maps from changes in haemodynamic responses from every point in the brain. Another 22% are region of interest studies examining the physiological properties of different brain structures, analogous to single-unit recordings; 8% are on neuropsychology; 5% on the properties of the fMRI signal; and the rest is on a variety of other topics including plasticity, drug action, experimental designs and analysis methods.

In humans, fMRI is used routinely not just to study sensory processing or control of action, but also to draw provocative conclusions about the neural mechanisms of cognitive capacities, ranging from recognition and memory to pondering ethical dilemmas. Its popular fascination is reflected in countless articles in the press speculating on potential applications, and seeming to indicate that with fMRI we can read minds better than direct tests of behaviour itself. Unsurprisingly, criticism has been just as vigorous, both among scientists and the public. In fact, fMRI is not and will never be a mind reader, as some of the proponents of decoding-based methods suggest, nor is it a worthless and non-informative 'neophrenology' that is condemned to fail, as has been occasionally argued.

Perhaps the extreme positions on both sides result from a poor understanding of the actual capacities and limitations of this technology, as well as, frequently, a confusion between fMRI shortcomings and potential flaws in modelling the organizational principles of the faculties under investigation. For example, a frequently made assumption is that the mind can be subdivided into modules or parts whose activity can then be studied with fMRI. If this assumption is false, then even if the brain's architecture is modular, we would never be able to map mind modules onto brain structures, because a unified mind has no components to speak of. Even if true, the challenge remains in coming up with the correct recursive decompositions—in each of which any given cognitive capacity, however abstract, is divided into increasingly smaller functional units that are localized to specific brain parts, which in turn can be detected and studied with fMRI. This is not a neuroimaging problem but a cognitive one. Hierarchical decompositions are clearly possible within different sensory modalities and motor systems. Their mapping, which reflects the brain's functional organization, is evidently possible and certainly meaningful beyond any reasonable doubt[1].

Here, I offer an assessment of fMRI methodology itself, leaving aside such epistemological and ontological issues. I take the modular organization of many brain systems as a well established fact, and discuss only how far fMRI can go in revealing the neuronal mechanisms of behaviour by mapping different system modules and their dynamic inter-relationships. In this context the term module captures the classical local neuronal circuits repeated iteratively within a structure (for example, the columns or swirling, slab-like tangential arrangements of the neocortex), as well as the entities within which modules might be grouped by sets of dominating external connections. The often used term functional segregation refers to such specialized and spatially separated modules. Segregated entities that are interconnected might further result in nested distributed systems, the activity of which, often termed functional integration, can only be visualized by large-scale neuroimaging.

The principal advantages of fMRI lie in its noninvasive nature, ever-increasing availability, relatively high spatiotemporal resolution, and its capacity to demonstrate the entire network of brain areas engaged when subjects undertake particular tasks. One disadvantage is that, like all haemodynamic-based modalities, it measures a surrogate signal whose spatial specificity and temporal response are subject to both physical and biological constraints. A more important

[1]Max Planck Institute for Biological Cybernetics, 72076 Tuebingen, Germany, and Imaging Science and Biomedical Engineering, University of Manchester, Manchester M13 9PL, UK.

shortcoming is that this surrogate signal reflects neuronal mass activity. Although this fact is acknowledged by the vast majority of investigators, its implications for drawing judicious conclusions from fMRI data are most frequently ignored. The aim of this review is first to describe briefly the fMRI technology used in cognitive neuroscience, and then discuss its neurobiological principles that very often limit data interpretation. I hope to point out that the ultimate limitations of fMRI are mainly due to the very fact that it reflects mass action, and much less to limitations imposed by the existing hardware or the acquisition methods. Functional MRI is an excellent tool for formulating intelligent, data-based hypotheses, but only in certain special cases can it be really useful for unambiguously selecting one of them, or for explaining the detailed neural mechanisms underlying the studied cognitive capacities. In the vast majority of cases, it is the combination of fMRI with other techniques and the parallel use of animal models that will be the most effective strategy for understanding brain function.

A brief overview of fMRI

The beautiful graphics MRI and fMRI produce, and the excitement about what they imply, often mask the immense complexity of the physical, biophysical and engineering procedures generating them. The actual details of MRI can only be correctly described via quantum mechanics, but a glimpse of the method's foundation can be also afforded with the tools of classical physics using a few simple equations. (See refs 2 and 3 for a comprehensive account of the theoretical and practical aspects of MRI, and ref. 4 for its functional variants.) Here I offer a brief overview that permits an understandable definition of the terms and parameters commonly used in magnetic resonance imaging (see 'MRI and fMRI principles' in the Supplementary Information for a description of the principles and terms of anatomical and functional MRI). Functional activation of the brain can be detected with MRI via direct measurements of tissue perfusion, blood-volume changes, or changes in the concentration of oxygen. The blood-oxygen-level-dependent (BOLD) contrast mechanism[5,6] is currently the mainstay of human neuroimaging.

Critical factors determining the utility of fMRI for drawing conclusions in brain research are signal specificity and spatial and temporal resolution. Signal specificity ensures that the generated maps reflect actual neural changes, whereas spatial and temporal resolution determine our ability to discern the elementary units of the activated networks and the time course of various neural events, respectively. The interpretability of BOLD fMRI data also depends critically on the experimental design used.

Spatiotemporal properties of BOLD fMRI. The spatiotemporal properties of fMRI are covered in some detail in the Supplementary Information. Briefly, spatial specificity increases with increasing magnetic field strength and for a given magnetic field can be optimized by using pulse sequences that are less sensitive to signals from within and around large vessels (see Fig. 1 and 'Spatial and temporal specificity' in the Supplementary Information). Spatiotemporal resolution is likely to increase with the optimization of pulse sequences, the improvement of resonators, the application of high magnetic fields, and the invention of intelligent strategies such as parallel imaging, for example, sensitivity encoding (SENSE) method (see 'Spatial resolution' section in the Supplementary Information).

Human fMRI can profit a great deal from the use of high-field scanners and by the optimization of the pulse sequences used. Surprisingly, only a minority of the studies in the cognitive sciences seem to exploit the technical innovations reported from laboratories working on magnetic resonance methodologies. Most of the top-cited cognitive neuroscience studies (approximately 70%) were carried out at 1.5 T scanners, 20% were carried out at 3 T scanners, and very few at 2 T or 4 T field strengths. About 87% of all studies used the conventional gradient-echo echoplanar imaging (GE-EPI), whereas the rest used different variants of the spin-echo echoplanar imaging (SE-EPI) sequence. This combination of low magnetic field and traditional GE-EPI is prone to many localization errors. However, as of the beginning of the twenty-first century the percentage of middle-field (3 T) studies has increased, to reach about 56% in 2007. High magnetic fields are likely to dominate magnetic resonance research

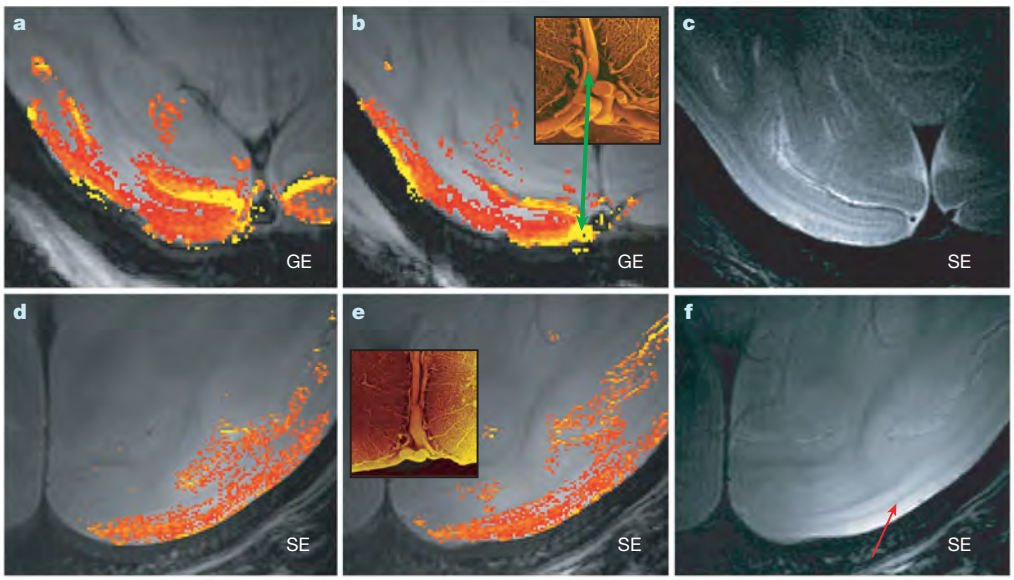

Figure 1 | Specificity of GE-EPI and SE-EPI. Examples of high-resolution GE-EPI and SE-EPI (courtesy J. Goense, MPI for Biological Cybernetics). **a**, **b**, Two slices of GE-EPI demonstrating the high functional signal-to-noise ratio (SNR) of the images, but also the strong contribution of macrovessels. The yellow areas (indicated with the green arrows) are pia vessels, an example of which is shown in the inset scanning electron microscopy image (total width of inset, 2 mm). For the functional images red indicates low and yellow indicates high. In-plane resolution 333 × 333 μm^2; slice thickness 2 mm. **c**, Anatomical scan, SE-EPI, 250 × 188 μm^2, 2 mm slice, with time to echo (TE) and repetition time (TR) 70 and 3,000 ms respectively. **d**, **e**, Two slices of SE-EPI showing the reduction of vascular contribution at the pial side of the cortex. In-plane resolution 250 × 175 μm^2, slice thickness 2 mm. **f**, The anatomical scan is the SE-EPI used for obtaining the functional scans (TE/TR = 48/2,000 ms) but at different greyscale and contrast. The resolution of the anatomical scan permits the clear visualization of the Gennari line (red arrow), the characteristic striation of the primary visual

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in different areas of cortex is anything but straightforward. In fact, we now know that the traditional cortical input–elaboration–output scheme, commonly presented as an instantiation of the tripartite perception–cognition–action model, is probably a misleading oversimplification[16]. Research shows that the subcortical input to cortex is weak; the feedback is massive, the local connectivity reveals strong excitatory and inhibitory recurrence, and the output reflects changes in the balance between excitation and inhibition, rather than simple feedforward integration of subcortical inputs[17]. In the context of this review, the properties of these excitation–inhibition networks (EIN) deserve special attention, and are briefly discussed below.

Feedforward and feedback cortical processing. Brain connectivity is mostly bidirectional. To the extent that different brain regions can be thought of as hierarchically organized processing steps, connections are often described as feedforward and feedback, forward and backward, ascending and descending, or bottom-up and top-down[18]. Although all terms agree on processing direction, endowing backward connections with a role of engineering-type or functional 'feedback' might occasionally be misleading, as under a theoretical generative model perspective on brain function, it is the backward connections that generate predictions and the forward connections that convey the traditional feedback, in terms of mismatch or prediction error signals[19].

In the sensory systems, patterns of long-range cortical connectivity to some extent define feedforward and feedback pathways[20]. The main thalamic input mainly goes to middle layers, whereas second-order thalamic afferents and the nonspecific diffuse afferents from basal forebrain and brain-stem are, respectively, distributed diffusely regionally or over many cortical areas, making synapses mainly in superficial and/or deep layers. Cortical output has thalamic and other subcortical projections originating in layers VI and V, respectively, and corticocortical projections mostly from supragranular layers. The primary thalamic input innervates both excitatory and inhibitory neurons, and communication between all cell types includes horizontal and vertical connections within and between cortical layers. Such connections are divergent and convergent, so that the final response of each neuron is determined by all feedforward, feedback and modulatory synapses[17].

Very few of the pyramid synapses are thalamocortical (less than 10–20% in the input layers of cortex, and less than 5% across its entire depth; in the primary visual cortex the numbers are even lower, with the thalamocortical synapses on stellate cells being about 5%[21]), with the rest originating from other cortical pyramidal cells. Pyramidal axon collateral branches ascend back to and synapse in superficial layers, whereas others distribute excitation in the horizontal plane, forming a strongly recurrent excitatory network[17].

The strong amplification of the input signal caused by this kind of positive feedback loop is set under tight control by an inhibitory network interposed among pyramidal cells and consisting of a variety of GABAergic interneurons[22,23]. These can receive both excitatory and inhibitory synapses on to their somata, and have only local connections. About 85% of them in turn innervate the local pyramidal cells. Different GABAergic cells target different subdomains of neurons[22,24]. Some (for example, basket cells) target somata and proximal dendrites, and are excellent candidates for the role of gain adjustment of the integrated synaptic response; others (for example, chandelier cells) target directly the axons of nearby pyramidal neurons, and appear to have a context-dependent role[25]—they can facilitate spiking during low activity periods, or act like gatekeepers that shunt most complex somatodendritic integrative processes during high activity periods (for example, see up- and down states below). Such nonlinearities might generate substantial dissociations between subthreshold population activity and its concomitant metabolic demand and the spiking of pyramidal cells.

Modules and their microcircuits. A large number of structural, immunochemical and physiological studies, in all cortical areas examined so far, suggested that the functional characteristics of a cortical module are instantiated in a simple basic EIN, referred to as a canonical microcircuit[17] (see also Fig. 2a). Activation of a microcircuit sets in motion a sequence of excitation and inhibition in every neuron of the module, rather than initiating a sequential activation of separate neurons at different hypothetical processing stages. Re-excitation is tightly controlled by local inhibition, and the time evolution of excitation–inhibition is far longer than the synaptic delays of the circuits involved. This means the magnitude and timing of any local mass activation arise as properties of the microcircuits.

Computational modelling suggested that EIN microcircuits, containing such a precisely balanced excitation and inhibition, can account for a large variety of observations of cortical activity, including amplification of sensory input, noise reduction, gain control[26], stochastic properties of discharge rates[27], modulation of excitability with attention[28], or even generation of persisting activity during the delay periods of working memory tasks[29].

The principle of excitation–inhibition balance implies that microcircuits are capable of large changes in activity while maintaining proportionality in their excitatory and inhibitory synaptic conductances. This hypothesis has been tested directly in experiments examining conductance changes during periods of high (up) and low (down) cortical activity. Alternating up states and down states can be readily observed in cerebral cortex during natural sleep or anaesthesia[30], but they can be also induced *in vitro* by manipulating the ionic concentrations in a preparation so that they match those found *in situ*. Research showed that the up state is characterized by persisting synaptically mediated depolarization of the cell membranes owing to strong barrages of synaptic potentials, and a concomitant increase in spiking rate, whereas the down state is marked by membrane hyperpolarization and reduction or cessation of firing[31,32]. Most importantly, the excitation–inhibition conductances indeed changed proportionally throughout the duration of the up state despite large changes in membrane conductance[31,32].

Microcircuits therefore have the following distinct features: (1) the final response of each neuron is determined by all feedforward, feedback and modulatory synapses; (2) transient excitatory responses may result from leading excitation, for example, due to small synaptic delays or differences in signal propagation speed, whereupon inhibition is rapidly engaged, followed by balanced activity[31,32]; (3) net excitation or inhibition might occur when the afferents drive the overall excitation–inhibition balance in opposite directions; and (4) responses to large sustained input changes may occur while maintaining a well balanced excitation–inhibition. In the latter case, experimentally induced hyperpolarization of pyramidal cells may abolish their spiking without affecting the barrages of postsynaptic potentials (see ref. 31 and references therein). It is reasonable to assume that any similar hyperpolarization under normal conditions would decrease spiking of stimulus-selective neurons without affecting presynaptic activity. In visual cortex, recurrent connections among spiny stellate cells in the input layers can provide a significant source of recurrent excitation[26]. If driven by proportional excitation–inhibition synaptic currents, the impact of their sustained activity might, once again, minimally change the spiking of the pyramidal cells. This last property of microcircuits suggests that changes with balanced excitation–inhibition are good candidates for mechanisms adjusting the overall excitability and the signal-to-noise ratio (SNR) of the cortical output. Thus microcircuits—depending on their mode of operation—can, in principle, act either as drivers, faithfully transmitting stimulus-related information, or as modulators, adjusting the overall sensitivity and context-specificity of the responses[28]. Figure 2b summarizes the different types of excitation-inhibition changes and their potential effect on the haemodynamic responses.

This interesting and important driver/modulator distinction was initially drawn in the thalamus[33], in which the afferents in the major sensory thalamic relays were assigned to one of two major classes on the basis of the morphological characteristics of the axon terminals, the synaptic relationships and the type of activated receptors, the

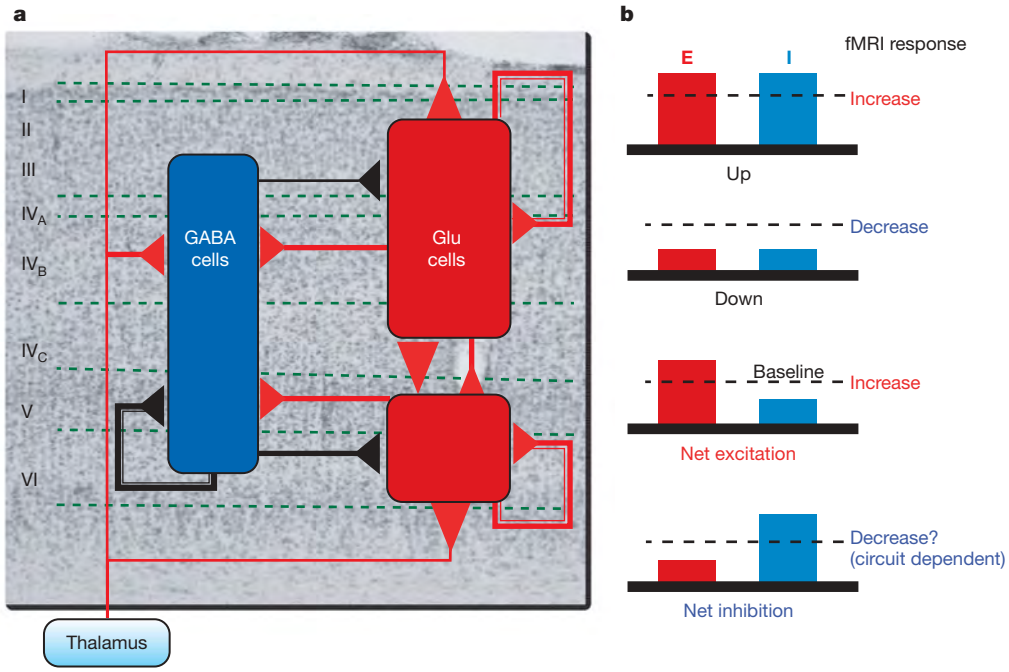

Figure 2 | Principles of excitation–inhibition circuits. a, Model of a canonical cerebral microcircuit (adapted from ref. 71). Three neuronal populations interact with each other: supragranular–granular and infragranular glutamatergic spiny neurons, and GABAergic cells. Excitatory synapses are shown in red and inhibitory synapses in black. All groups receive excitatory thalamic input. The line width indicates the strength of connection. The circuit is characterized by the presence of weak thalamic input and strong recurrence (see text for details). Glu, glutamatergic. **b**, Potential proportional and opposite-direction changes of cortical excitation (E) and inhibition (I). Responses to large sustained input changes may occur while maintaining a well balanced excitation–inhibition (up and down). The commonly assumed net excitation or inhibition might occur when the afferents drive the overall excitation–inhibition balance in opposite directions. The balanced proportional changes in excitation–inhibition activity, which occur as a result of neuromodulatory input, are likely to strongly drive the haemodynamic responses.

degree of input convergence, and the activity patterns of postsynaptic neurons. The same concept also broadly applies to the afferents of the cerebral cortex[34], wherein the thalamic or corticocortical axons terminating in layer IV can be envisaged as drivers, and other feedback afferents terminating in the superficial layers as modulators. It can also be applied to the cortical output, whereby the projections of layer VI back to the primary relays of the thalamus are modulatory, whereas the cortico-thalamo-cortical paths originating in layer V of cortex, reaching higher-order thalamic nuclei (for example, pulvinar), and then re-entering cortex via layer IV, are drivers[33].

The initial information reaching a cortical region is elaborated and evaluated in a context-dependent manner, under the influence of strong intra- and cross-regional cortical interactions. The cortical output reflects ascending input but also cortico-thalamo-cortical pathways, whereas its responsiveness and SNR reflect the activity of feedback, and likely input from the ascending diffuse systems of the brain-stem. The neuromodulation (see 'Neurotransmission and neuromodulation' in Supplementary Information) afforded by these systems, which is thought to underlie the altered states of cognitive capacities, such as motivation, attention, learning and memory, is likely to affect large masses of cells, and potentially induce larger changes in the fMRI signal than the sensory signals themselves.

Excitation–inhibition networks and fMRI. The organization discussed above evidently complicates both the precise definition of the conditions that would justify the assignment of a functional role to an 'active' area, and interpretation of the fMRI maps. Changes in excitation–inhibition balance—whether they lead to net excitation, inhibition, or simple sensitivity adjustment—inevitably and strongly affect the regional metabolic energy demands and the concomitant regulation of cerebral blood flow (CBF) (that is, they significantly alter the fMRI signal). A frequent explanation of the fMRI data simply assumes an increase in the spiking of many task- or stimulus-specific neurons. This might be correct in some cases, but increases of the BOLD signal may also occur as a result of balanced proportional increases in the excitatory and inhibitory conductances, potential concomitant increases in spontaneous spiking, but still without a net excitatory activity in stimulus-related cortical output. In the same vein, an increase in recurrent inhibition with concomitant decreases in excitation may result in reduction of an area's net spiking output, but would the latter decrease the fMRI signal? The answer to this question seems to depend on the brain region that is inhibited, as well as on experimental conditions.

Direct haemodynamic measurements with autoradiography suggested that metabolism increases with increased inhibition[35]. An exquisite example is the inhibition-induced increase in metabolism in the cat lateral superior olive (LSO). This nucleus, which contains the representations of low-, middle- and high-tone frequencies, receives afferents from both ears: over a two-neuron pathway from the ipsilateral ear and over a three-neuron pathway from the contralateral ear. Furthermore, it has no presynaptic axo-axonic endings that might mediate presynaptic inhibition via excitatory terminals. Electrophysiology showed that the LSO afferents from the ipsilateral ear are excitatory whereas the afferents from the contralateral ear are inhibitory. This unusual combination of anatomical and physiological features suggests that if one ear is surgically deafened and the animal is exposed to a high-frequency pure tone, a band of tissue in the LSO on the side opposite to the remaining active ear is subjected to strictly inhibitory synaptic activity without complications by presynaptic inhibition, concurrent lateral excitation, disinhibition/excitation, or other kinds of possibly excitatory action. Under these conditions, maps obtained with [^{14}C]2-deoxyglucose (2DG) autoradiography[36] demonstrated clear increases in metabolism in the contralateral LSO[37], suggesting that the presynaptic activity in that area is sufficient to show strong energy consumption despite the ensuing spiking reduction. Similar increases in metabolism during the reduction of spike rates were observed during long-lasting microstimulation of the fornix, which induces sustained suppression of pyramidal cell firing in hippocampus[38].

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In contrast, human fMRI studies reported haemodynamic and metabolic downregulation accompanying neuronal inhibition in motor[39] and visual cortices[40], suggesting that the sustained negative BOLD response (NBR) is a marker of neuronal deactivation. Similarly, combined fMRI and electrophysiological experiments showed a clear correspondence of NBR and decreased population spiking in haemodynamically 'negative' areas in the monkey primary visual cortex[41]. Decreases in blood oxygenation and volume were also found to be co-localized with predominant neuronal inhibition and arteriolar vasoconstriction during somatosensory stimulation in rats[42]. Thus, without understanding the intrinsic correlation between direct or indirect inhibitory activity and concomitant changes in energy metabolism in a given situation, conclusions cannot be drawn. Unfortunately, the few published theoretical estimates of energy budget have not considered the metabolic costs of spikes in interneurons and of the inhibitory postsynaptic potentials (IPSPs) they produce[43]. Modelling of inhibition is unlikely to be straightforward. On the one hand, the density of cortical inhibitory neurons is 10–15 times lower than excitatory neurons[16], and for each one of them the electrochemical gradient, down which Cl^- moves postsynaptically at inhibitory synapses, is weaker than that of Na^+ at excitatory synapses, requiring less energy to pump Cl^- back. In fact, the transport cycles of the cation–chloride co-transporters, which have a key role in intracellular Cl^- regulation, are driven without the direct hydrolysis of ATP, by using the energy from the cation gradients generated by the Na,K-ATPase[44]. On the other hand, inhibitory interneurons are fast spiking[45,46]. For example, the firing of pyramidal cells in hippocampus is 1.4 Hz, whereas that of interneurons in the strata pyramidale and oriens is 15 Hz and 10 Hz, respectively. Similarly, cortical inhibitory interneurons may discharge 2–3 times faster than pyramidal cells[47]. In principle, inhibition may increase or decrease energy consumption depending on the contribution of the aforementioned factors (for a recent comprehensive review on inhibitory neurons and brain metabolism, see ref. 48). Last but not least, neurons directly affect microvessels. Pericytes, the flat, contractile connective-tissue cells, often attached to the abluminal surface of the capillary endothelial cells, might directly alter CBF in response to changes in neural activity[49]. Moreover, a body of evidence suggests that increased activity of single inhibitory interneurons results in precise vasomotor responses in neighbouring brain microvessels, and these contractile or dilatory responses were attributed to arteriole smooth muscle[50].

The diversity of the haemodynamic responses to neural inhibition obtained in different types of experiments is therefore hardly surprising: it is primarily due to the fact that regional inhibition itself might have a number of different causes, including early shunting of the weak cortical input, leading to a reduction of recurrent excitation rather than an increase in summed inhibition; increased synaptic inhibition; shunting of the cortical output through the axo-axonic connections of the chandelier cells; or any combination thereof. In the first case inhibition might result in a clear NBR; in the other two it might reflect the local metabolism increases induced by the unaffected input and its ongoing processing, resulting in fMRI activations. The fMRI responses might further blur the origin of inhibition owing to the direct effects of the latter on the arterioles and microvessels.

Evidently much research is needed to characterize the actual state of an area and its participation in behaviour, but quite independent of this fact, the nature of the EIN suggests that mass action and its surrogate haemodynamics are ambiguous signals, the interpretation of which must be constrained by the concurrent use of other methodologies.

Neurophysiological correlates of the BOLD signal

EIN and mesoscopic neural signals. The active regions of the membrane of a discharging neuron at any given time are considered to act as a current sink, whereas the inactive ones act as a current source for the active regions (see 'Neural signals' in Supplementary Information). The linear superposition of currents from all sinks and sources forms the extracellular field potential measured by microelectrodes. The extracellular field potential captures at least three different types of EIN activity: single-unit activity representing the action potentials of well isolated neurons next to the electrode tip, multiple unit activity reflecting the spiking of small neural populations in a sphere of 100–300 μm radius, and perisynaptic activity of a neural population within 0.5–3 mm of the electrode tip, which is reflected in the variation of the low-frequency components of the extracellular field potential. Multiple unit activity and local field potentials (LFPs) can be reliably segregated by frequency band separation. A high-pass filter cutoff in the range of 500–1,000 Hz is used in most recordings to obtain the multiple unit activity, and a low-pass filter cutoff of approximately 250 Hz to obtain LFP. A large number of experiments have presented data indicating that such a band separation does indeed underlie different neural events (see 'Neural signals' in Supplementary Information).

LFP signals and their different band-limited components (alpha, beta, gamma, and so on) are invaluable for understanding cortical processing, as they are the only signs of integrative EIN processes. In fact, LFPs do not, as initially thought, solely reflect population postsynaptic potentials, but also integrative soma–dendritic processes—including voltage-dependent membrane oscillations and afterpotentials following soma–dendritic spikes—that all together represent the local (perisynaptic) activity in a region (see 'Neural signals' in Supplementary Information). A shortcoming of the LFP is its ambiguity. A change in the power of LFP in a particular frequency band most likely occurs for any mode of operations of the EIN. As most of the excitatory input into an area is local, LFPs will also indirectly reflect some of the postsynaptic effects of pyramidal cell activity. In addition, LFPs have a certain neural-class bias, which in this case is determined by geometry and regional architecture. The arrangement of the pyramidal and Purkinje cells will give rise to large LFP modulations; in contrast, interneurons will contribute only weakly because of their star-shaped dendrites and their geometrical disorder. Finally, inhibitory synapses may occasionally act as 'shunts' for the excitatory currents through low-resistance channels, in which case large synaptic conductance changes may produce little effect in the membrane potential, and result in weak and hard-to-measure multiple unit activity and LFPs.

When individual LFP bands are examined separately, local spiking activity is occasionally found to affect certain frequency bands, whereas that of neuromodulation affects others[51–53]. It is evident that the most useful information will not be derived by one type of signal alone, but rather by the study of relative changes in one signal or the other. Electrophysiological studies examining the individual contributions of different LFP frequency bands, multiple unit activity, and spiking of individual neurons are probably our only realistic chance of gaining insights into the neural mechanisms of haemodynamic responses and their meaning in the context of different cognitive tasks.

Mesoscopic signals and the BOLD signal. The relationship of neocortical LFPs and spiking activity to the BOLD signal itself was examined directly in concurrent electrophysiology and fMRI experiments in the visual system of anaesthetized[54] and alert[55] monkeys. These studies found that the BOLD responses reflect input and intracortical processing rather than pyramidal cell output activity. Initially, both LFPs and spiking seemed to be correlated with the BOLD response, although quantitative analysis indicated that LFPs are better predictors of the BOLD response than multiple-unit or single-unit spiking. The decisive finding leading to the papers' conclusion, however, was not the degree of correlation between the neural and the fMRI responses or the differential contribution of any type of signal into the BOLD responses[55], but rather the striking, undiminished haemodynamic responses in cases where spiking was entirely absent despite a clear and strong stimulus-induced modulation of the field

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potentials[54,55]. Similar dissociations between spikes and CBF had been demonstrated earlier and very recently in a number of studies using other techniques[56–58].

The findings are in close agreement with a number of older autoradiography studies, also showing that regional glucose utilization is directly related to neuronal synaptic activity[35]. For example, the greatest 2-DG uptake occurs in the neuropil (that is, in areas rich in synapses, dendrites and axons, rather than in cell bodies). During orthodromic and antidromic electrical microstimulation, only orthodromic microstimulation, which involves presynaptic terminals, increases glucose consumption. Similarly, the highest density of cytochrome oxidase (an enzyme of the respiratory chain) is found in somato-dendritic regions that are adjacent to axon terminals. Finally, as mentioned earlier, presynaptic activity increases metabolism even if the output is inhibited (that is, the spiking activity is abolished).

Despite all this evidence, some discussion still concentrates on the importance of the firing rate of action potentials of projection neurons in the generation of the haemodynamic responses, perhaps stemming from the fact that important early studies of neural correlates of behaviour took the mean spiking rate to be the gold standard for quantifying neuronal activation. These discussions, however, often suffer from a certain amount of contention seeking where none is warranted. In many cases, spikes do indeed correlate with LFPs, and they will also correlate with the BOLD signal. In addition, unusually high correlations between multiple unit activity and BOLD signal (or LFP and multiple unit activity) may result from excessive signal-smoothing owing to sampling rates of several seconds rather than a fraction of a second, as well as inter-subject averaging when simultaneous physiology and fMRI measurements are not possible (see ref. 55 for discussion).

Predicting neural activity from the fMRI signals. Functional MRI signals are presumed to result from changes in the activity of the neuronal populations responsible for the functions in question (for example, stimulus- or task-selective neurons). This assumption is mainly based on decades of electrophysiology research with recordings from isolated single neurons in experimental animals, in which particular sensory stimuli that the animal perceives or tasks that it performs were found to increase the firing rate of certain cells but not of others. The psychologist or cognitive neuroscientist who finds cortical area X to be activated by the task at hand implicitly or explicitly assumes that—if an electrode were placed in the subject's brain—an increase in the spiking rate of those specialized neurons underlying the subject's behaviour would be observed. This might well be true in some cases, but not in all. When attempting to interpret the fMRI signal by modelling, or when comparing the results of human neuroimaging to those obtained in monkey physiology experiments, it is useful to take the following facts into consideration.

In humans, there are about 90,000–100,000 neurons under 1 mm^2 of cortical surface. This number is relatively constant for all structurally and functionally distinct areas, including the somatosensory, temporal, parietal, frontal and motor cortical areas[16,59]. An exception is the primary visual cortex of certain primates, including monkey and human, which has approximately twice as many neurons. The number of cortical neurons under unitary cortical surface is also similar across many species, including mouse, rat, cat, monkey and human. Its small variability is the result of a trade-off between cortical thickness and neural density. The former varies from area to area and from species to species (for example, from mouse to human the cortex becomes approximately three times thicker). Neural density varies inversely to cortical thickness. On average, density is 20,000 to 30,000 neurons per mm^3; it peaks in the primary visual cortex by a factor of 4, and it is minimal in the motor cortex[59,60]. Synaptic density ranges from 0.4 to 1×10^9 per mm^3. Depending on the thickness of the cortex (2–4 mm), the number of synapses beneath 1 mm^2 surface is around 10^9 ($0.8–4 \times 10^9$). Although the number of synapses and the axonal length per neuron increases with increasing cortical thickness[61], the overall length of neuronal processes remains relatively constant, with axonal length being approximately 4 km mm^{-3} and dendrite length 0.4 km mm^{-3}. Overall, synaptic density and the ratio of excitatory to inhibitory synapses also remain constant.

Given these neuro-statistical data, what are the actual contents of a neuroimaging voxel? An examination of the 300 top-cited cognitive fMRI studies suggests that the commonly used in-plane resolution is 9–16 mm^2, for slice thicknesses of 5–7 mm. The average voxel size before any pre-processing of the data is thus 55 μl (or 55 mm^3). Often the effective size is 2–3 times larger due to the spatial filtering that most investigators apply to improve the functional SNR. Less than 3% of this volume is occupied by vessels and the rest by neural elements (see Fig. 3) A typical unfiltered fMRI voxel of 55 μl in size thus contains 5.5 million neurons, $2.2–5.5 \times 10^{10}$ synapses, 22 km of dendrites and 220 km of axons.

This 'large population view' is in contrast to the scope of the traditional microelectrode recordings. It would be nice if we could monitor every relevant neuron in the cortex during intracortical microelectrode recordings, but this is practically impossible. Instead, the typical electrophysiological measurements in behaving animals report only on the properties of most active large neurons that constitute a minority. The strong selection bias during extracellular recordings is partly due to practical limitations (for example, injury or simply size bias[62]) and partly to the physiological properties of neurons and/or the organizational principles of neural networks. In fact, many different types of electrical and optical measurements provide evidence that a substantial proportion of neurons, including the cortical pyramidal cells, might be silent[63]. Their silence might reflect unusually high input selectivity or the existence of decoding schemes relying on infrequent co-spiking of neuronal subsets. Most important for the comparison of neuroimaging and electrophysiology results is the fact that lack of measurable neuronal spiking may not necessarily imply lack of input and subthreshold processing.

A direct analogy between neuronal spiking as measured in animal experiments and the fMRI signal obtained in human recording is thus simply unrealistic and might often lead to incorrect conclusions. It is hardly surprising that most studies so far relying purely on BOLD fMRI have failed to reveal the actual neural properties of the studied area, at least those properties (for example, selectivity to various visual features) that were previously established in electrophysiological studies.

An example is cortical area V5 (or MT) that has been extensively studied in the context of motion processing and perception[64,65]. Electrophysiology has shown that the vast majority of the V5 neurons in monkeys are direction and speed selective. Neuroimaging localized the homologue of area V5 in humans as an area responding stronger to moving than to stationary stimuli. Later studies suggested that human V5 is sensitive to motion direction, and that it may be thought of as containing large populations of directionally selective units, just like its monkey homologue. The studies of directional specificity exploited the phenomenon of motion after-effect induced by motion adaptation. After prolonged exposure to a stimulus moving in one direction, subjects perceive a subsequent static stimulus to move in the opposite direction. It is assumed that motion after-effect is due to the fact that the balance of mutual inhibition (opponency) between detectors for opposite directions of movement is distorted after adaptation. The sensitivity of the detectors selective for the adapting direction is reduced, which in turn releases from inhibition the neurons selective for the opposite direction[66]. Using this phenomenon, human studies demonstrated that the fMRI response to a stationary stimulus was greater when the stimulus was preceded by a motion-after-effect-inducing, unidirectional adaptation, than when preceded by bidirectional adaptation[67]. Given the existing physiology data in the monkey V5, these findings were interpreted as demonstrating that the BOLD signal directly reflects direction-selective spiking activity of the area.

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Yet, as I have indicated above, the BOLD signal is primarily affected by changes in excitation–inhibition balance, and this balance may be controlled by neuromodulation more than by the changes in spiking rate of a small set of neurons. In fact, the BOLD signal is strongly modulated by attention[68], and the results of the motion after-effect experiments could, in principle, be due to the fact that a stimulus with illusory motion automatically draws the attention of a subject more compared to a situation in which there is no motion after-effect. This hypothesis turned out to be correct, as a later study—in which balance in attentional load was accomplished by having the subjects perform a concurrent visual task—found no signal differences between the motion after-effect and no motion after-effect conditions[69].

A similar example pertains to the differences in neurophysiological and fMRI responses in the primary visual cortex during different perceptual states. It is known that physiological signals are in general stronger when stimuli are perceived as opposed to when they are not. Intriguingly, in some regions the BOLD response seems to reflect this even more sensitively than physiological measures like spikes and multi-unit activity[70]. An example is the pattern of fMRI activation changes in V1 during binocular rivalry (that is, the perceptual alternations experienced when the two eyes view different stimuli). This phenomenon has been studied extensively psychophysically and also over the last two decades in a series of electrophysiology studies in monkeys[70]. These studies showed that only a small fraction of V1 cells modulate their spiking during the perceptual changes; neuroimaging, on the other hand, demonstrated fMRI-signal modulations that were nearly as large as those obtained during the physical alternation of stimuli[70]. The difference, once again, reflects the fact that neuromodulatory feedback from higher areas can be easily detected by means of fMRI, but not through the measurement of single-unit activity. Interestingly, measurements of subthreshold activity in another study of perceptual multistability revealed perception-related modulations in LFP, despite the unaltered spike rates[53]. Such clear spiking and BOLD signal mismatches appear even in simple experiments probing sensory processing. Simple stimuli, such as those used in the aforementioned studies, are most likely to generate a proportional enhancement in both the afferent and efferent activity of any sensory area. The activation of high-level association areas related to cognitive processing might be more sensitive or even dominated by feedback and neuromodulation, whose differential effect on spiking and haemodynamic responses is utterly unknown.

Conclusions and perspectives

The limitations of fMRI are not related to physics or poor engineering, and are unlikely to be resolved by increasing the sophistication and power of the scanners; they are instead due to the circuitry and

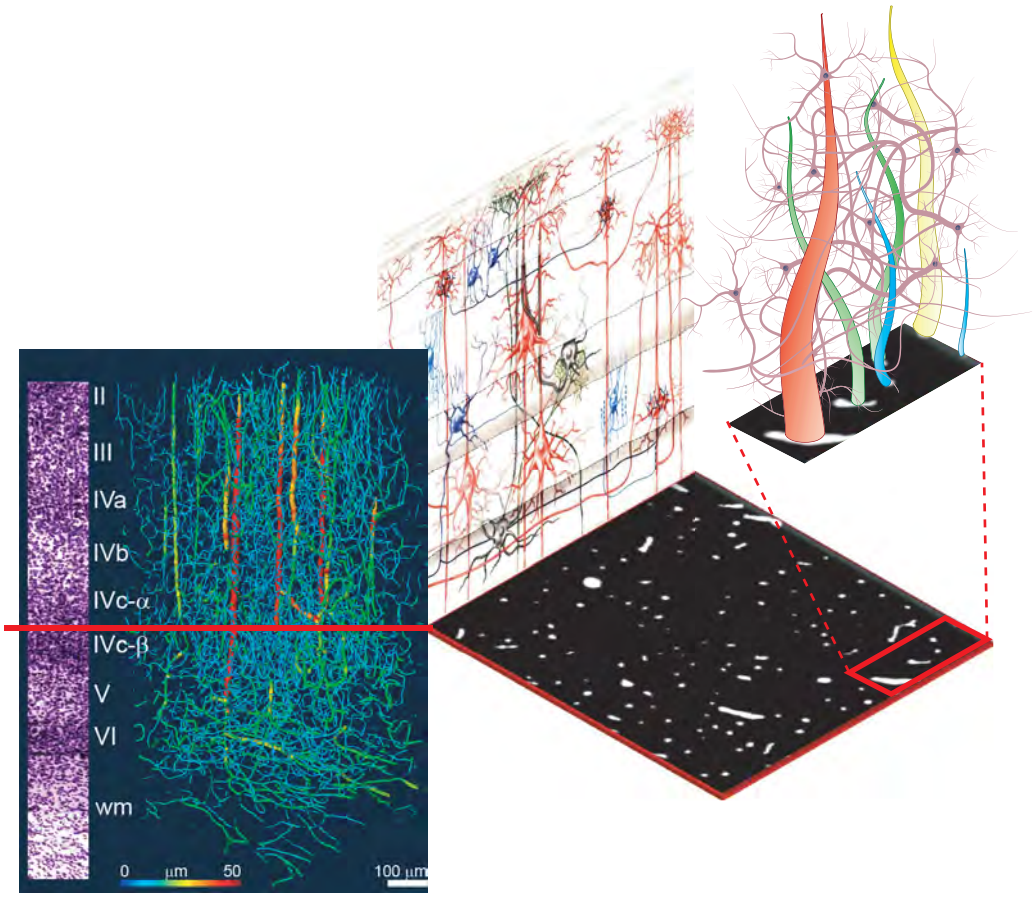

Figure 3 | Neural and vascular contents of a voxel. The left panel demonstrates the relative density of vessels in the visual cortex of monkeys. The dense vascular mesh is displayed by perfusing the tissue with barium sulphate and imaging it with synchrotron-based X-ray microtomography (courtesy B. Weber, MPI for Biological Cybernetics). The vessel diameter is colour coded. Cortical surface without pial vessels is displayed at the top; white matter at the bottom. At the left of the panel is a Nissl slice from the same area, showing the neural density for layers II through to the white matter (wm). Although the density of the vessels appears to be high in this three-dimensional representation, it is actually less the 3% (see section at the right; white spots are cross-sections of vessels). The average distance between the small vessels (capillaries) is about 50 μm. This is approximately the distance that oxygen molecules travel by diffusion within the limited transit time of the blood. The dense population of neurons, synapses and glia occupy the intervascular space, as depicted in the drawing at the top right—a hypothetical distribution of vascular and neural elements in a small section (red rectangle). The drawing in the background shows some of the typical neuronal types (for example, red, large pyramidal cell; dark blue, inhibitory basket cells; light blue, chandelier inhibitory neurons; and grey, stellate cells) and their processes.

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functional organization of the brain, as well as to inappropriate experimental protocols that ignore this organization. The fMRI signal cannot easily differentiate between function-specific processing and neuromodulation, between bottom-up and top-down signals, and it may potentially confuse excitation and inhibition. The magnitude of the fMRI signal cannot be quantified to reflect accurately differences between brain regions, or between tasks within the same region. The origin of the latter problem is not due to our current inability to estimate accurately cerebral metabolic rate of oxygen ($CMRO_2$) from the BOLD signal, but to the fact that haemodynamic responses are sensitive to the size of the activated population, which may change as the sparsity of neural representations varies spatially and temporally. In cortical regions in which stimulus- or task-related perceptual or cognitive capacities are sparsely represented (for example, instantiated in the activity of a very small number of neurons), volume transmission (see Supplementary Information)—which probably underlies the altered states of motivation, attention, learning and memory—may dominate haemodynamic responses and make it impossible to deduce the exact role of the area in the task at hand. Neuromodulation is also likely to affect the ultimate spatiotemporal resolution of the signal.

This having been said, and despite its shortcomings, fMRI is currently the best tool we have for gaining insights into brain function and formulating interesting and eventually testable hypotheses, even though the plausibility of these hypotheses critically depends on used magnetic resonance technology, experimental protocol, statistical analysis and insightful modelling. Theories on the brain's functional organization (not just modelling of data) will probably be the best strategy for optimizing all of the above. Hypotheses formulated on the basis of fMRI experiments are unlikely to be analytically tested with fMRI itself in terms of neural mechanisms, and this is unlikely to change any time in the near future.

Of course, fMRI is not the only methodology that has clear and serious limitations. Electrical measurements of brain activity, including invasive techniques with single or multiple electrodes, also fall short of affording real answers about network activity. Single-unit recordings and firing rates are better suited to the study of cellular properties than of neuronal assemblies, and field potentials share much of the ambiguity discussed in the context of the fMRI signal. None of the above techniques is a substitute for the others. Today, a multimodal approach is more necessary than ever for the study of the brain's function and dysfunction. Such an approach must include further improvements to MRI technology and its combination with other non-invasive techniques that directly assess the brain's electrical activity, but it also requires a profound understanding of the neural basis of haemodynamic responses and a tight coupling of human and animal experimentation that will allow us to fathom the homologies between humans and other primates that are amenable to invasive electrophysiological and pharmacological testing. Claims that computational methods and non-invasive neuroimaging (that is, excluding animal experimentation) should be sufficient to understand brain function and disorders are, in my opinion, naive and utterly incorrect. If we really wish to understand how our brain functions, we cannot afford to discard any relevant methodology, much less one providing direct information from the actual neural elements that underlie all our cognitive capacities.

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What we can do and what we cannot do with fMRI

Nikos K. Logothetis[1]

[1]Max Planck Institute for Biological Cybernetics, 72076 Tuebingen, Germany, and Imaging Science and Biomedical Engineering, University of Manchester, Manchester M13 9PL, UK.

MAGNETIC RESONANCE IMAGING

MRI Principles

There are many textbooks that thoroughly cover the theoretical and practical aspects of MRI (e.g.[38,108]) and its functional variants[11,48,69]. This brief overview is only given to provide an understandable definition of the terms and parameters commonly used in MR and fMR imaging.

Many nuclei possess a quantum mechanical property called spin, which can be most easily thought of as a tiny spinning magnet. For the purpose of this introduction we consider only spin-½ nuclei like the water and fat protons in biological tissues that dominate the signals measured in conventional MRI. Normally spins are randomly oriented; when an external magnetic field ***B_0*** is applied, however, the spins orient themselves according to the magnetic field, i.e. they start to precess around the axis of the magnetic field (think of the motion of a gyroscope or spinning top). Because the parallel alignment with the external field is energetically more favorable than the antiparallel state, there will be a net excess of spins aligned with the field; i.e. the spin system can be represented by a ***magnetization vector***. The difference between the number of parallel and antiparallel spins follows a Boltzmann distribution and increases with field strength. This difference in population is small, on the order of one in 10,000 000 spins at 1.5T, and NMR (***nuclear magnetic resonance***) is actually considered an insensitive technique. The spins precess according to the ***Larmor frequency*** (ω), which is related to the field through the ***gyromagnetic ratio*** (γ) (i.e. $\omega = \gamma * B_0$).

When a radiofrequency (RF) field of amplitude ***B_1*** rotating synchronously with the precessing spins is applied, the magnetization vector rotates away from its initial equilibrium position (aligned along the z-direction) by 90 degrees into the transverse (i.e. xy) plane, i.e. the longitudinal magnetization is converted to transverse magnetization. This happens only when the carrier frequency of the RF pulse is equal to the Larmor frequency, hence the term ***magnetic resonance***. While on the transverse plane, the magnetization can be detected by an RF receiver coil.

The application of B_1 not only equalizes the populations of spins in the two energy levels, but also introduces phase coherence among the spins. Coherence decreases quickly as the magnetic moments move out of phase as a result of their mutual interaction. The transverse magnetization, in other words, is short-lived; it decays exponentially as a result of processes known as ***relaxation***. There are different kinds of relaxation processes known as ***T_1, T_2, or T_2*,*** each reflecting different interactions of the spins with their environment or with other spins, and each specified by its time constant (T_i) or its inverse, the relaxation rate ($R_i = 1/T_i$). These relaxation rates differ depending on the properties of the tissue, and these differences are the basis of image contrast.

In biological and clinical sciences, most MRI signals are derived from the hydrogen nuclei of water, as the latter is the most abundant component (70-90%) of living tissues. The gyromagnetic ratio of protons is 42.58 MHz/Tesla, which means that the typical clinical magnet of 1.5T has a resonance frequency of approximately 64MHz, while a 7T magnet has a frequency of about 300 MHz. Field strength and frequency can be used

interchangeably to characterize the strength of a scanner (the former term is preferred in clinical research and fMRI and the latter in chemistry).

To generate an MR image, say an anatomical image of the brain, one needs a contrast mechanism that can separate different brain parts from one another (e.g. gray from white matter or from cerebrospinal fluids), and a mechanism by virtue of which that contrast can be calculated for each single volume element, commonly termed as ***MRI voxel***.

MRI contrast can be generated from a number of different quantities, including regional ***spin density***, ***water diffusion***, or the ***relaxation times*** mentioned above. Most MR images in biomedicine rely on a clever selection of acquisition parameters that make the image differentially sensitive (also called ***weighted***) to the relaxation process. It is impressive indeed to see how the choice of these simple parameters affects the contrast between the various tissues of the brain. For example, the usual anatomical images of the brain are most often T_1-weighted images, exploiting the differences in T_1 of gray and white matter.

Just as relaxation-rate differences at different sites might be used to generate ***anatomical contrast***, changes over time in one or more relaxation rates at a single site might be exploited to image changes in the physical-chemical state. This very simple principle underlies the ***functional contrast*** in fMRI, which often uses T_2^*-weighted imaging to detect changes in relaxation times (T_2^*) brought about by differences in blood oxygenation between test and control epochs.

Spatial localization, on the other hand, is achieved with the use of smaller magnetic field gradients that are superimposed on the homogenous magnetic field of the scanner and by subsequently exploiting the aforementioned Larmor relationship. According to the latter, the positions of protons within a voxel at different positions along the gradient field are encoded by their differences in resonance frequency.

Conventional MR imaging does not measure the signal decay immediately after the RF pulse. Instead, the decaying signal is “recovered” to some extent by ***refocusing*** the dephasing spins with additional RF pulses or by appropriately changing the magnetic field gradients used for spatial localization. The time between the peak of the RF excitation pulse and that of the recovered signal, i.e. the echo, is termed ***echo time (TE).*** Together with the ***repetition time (TR)*** these two parameters characterize the contrast and quality of an MR image. The combination of different types of RF and gradient pulses used to obtain the desired MR image is known as a ***pulse sequence***. There are very many different pulse sequences, but two are most often used in cognitive applications: ***gradient-recalled echo (GRE or GE)*** and ***spin echo (SE)***. They differ in the way they refocus the dephasing spines, whereby the former increases the coherence of precession of spins via gradient reversals, and the latter by means of RF pulses.

The type of information obtained from the usual MR images depends on the parameters just described. Pulse sequences whose TR is much longer than the longitudinal relaxation times T_1 and whose TE is much shorter than T_2 are typically used to obtain spin-density images. The usual anatomical images are obtained with pulse sequences having a TR value less or equal to T_1 and a TE value that is much shorter than the transverse relaxation time T_2. Using TR values that are much longer than T_1 and TE values that are equal to or larger than T_2 or T_2*, on the other hand, produces T_2- and T_2*-weighted images, respectively, such as those used in functional imaging. Nonetheless, when high temporal resolution is of importance, the TR in functional imaging can be even shorter than T_1.

Finally, an image can be acquired by using multiple excitation pulses, but also following a single RF pulse with a method known as ***echo planar imaging or EPI***[85]. Two types of EPI are most commonly used: ***spin-echo (SE-EPI)*** and ***gradient-echo (GE-EPI)*** echoplanar imaging. They differ in the way they refocus the spins prior to data acquisition, and they can be fine-tuned to yield the T_2- and T_2*-weighted images used in functional neuroimaging.

Functional MRI

Fortuitously, the physical and chemical events underlying the relaxation-rate changes can reflect alterations of neural activity in a reliable way. Relaxation rates may be affected by spin motion (e.g. blood flow), diffusion, or by changes in field homogeneity. Correspondingly, functional activations in the brain can be detected with MRI via direct measurements of ***tissue perfusion***[17], ***blood***

oxygenation[73], ***blood volume***[8], or reportedly even ***water diffusion***[58].

The first demonstration of the capacity of MRI to map cortical activation through hemodynamics was accomplished using the clinically well-established intravascular contrast agent Magnevist. When the blood-brain barrier (BBB) is intact, this lanthanide-gadolinium chelate, Gd-DTPA, is confined to the intravascular space, and this compartmentalization is the basis of the observed magnetic susceptibility effects in the surrounding tissues. Following an intravenous bolus injection, Magnevist produces significant signal changes during first-pass cerebral transit. Rapid imaging techniques detecting susceptibility differences in tissues (e.g. gradient-echo echo-planar imaging GE-EPI) can detect signal decreases during the passage of the intravascular agent through the capillary bed, and accurate estimates of the ***regional cerebral blood volume (rCBV)*** can be made by integrating over the first passage of the agent[84].

In their seminal study, Belliveau and his colleagues at Harvard University investigated the visual cortex of human subjects looking at a flickering visual pattern that was known to produce large hemodynamic changes. Regional CBV maps of the visual cortex in resting and activated states were obtained[8]; when these were superimposed on high-resolution anatomical images, the activated cortical regions were precisely delineated, demonstrating the potential of the technique to map brain areas involved in sensory stimulation, and potentially in cognitive processing as well. Shortly after this ***CBV-fMRI*** experiment three groups simultaneously and independently published the first functional maps of the human brain based on an endogenous intravascular contrast agent, the ***deoxyhemoglobin (dHb)*** of the blood[5,57,77].

The functional images utilized the ***blood-oxygen-level-dependent (BOLD)*** contrast, which depicts differences in blood oxygenation. This phenomenon was discovered by *Seiji Ogawa*, who noticed that the contrast of very high resolution brain images ($65x65x700\mu m^3$) acquired with GE pulse sequences depicts numerous dark lines of varying thickness. These lines were invisible when SE sequences were used, and they turned out to be signal dropouts from blood vessels[74]. Shortly thereafter, this effect was demonstrated in the cat brain during the course of experimentally induced anoxia[100].

Most neuroimaging today relies on signal variations induced by such local changes in field homogeneity. In biological samples inhomogeneities are induced by different materials that respond differently to the scanner field. Molecules like water weakly counteract the applied magnetic field and are known as ***diamagnetic***; in contrast, molecules like gadolinium compounds slightly enhance the magnetic field and are called ***paramagnetic***. The proximity of paramagnetic substances decreases T_2^*. An inhomogeneous distribution of paramagnetic materials introduces a field distortion into an MRI image known as ***susceptibility artifact***.

Almost all non-invasive fMRI is possible because the hemoglobin of the blood - which is sequestered in the blood red cells and thus inhomogeneously distributed in the tissues - is diamagnetic when it is oxygenated and paramagnetic when it is reduced, an effect first described by Linus Pauling and his student Coryell[79], who used a simple apparatus consisting of a wire, a glass tube, a balance, and a small electromagnet! The wire was suspended from one arm of the balance and held the tube that was placed between the electromagnet poles. They filled it with cattle blood, balanced it, and measured its weight. Passing an electric current through the coils changed the apparent weight, and this change was proportional to the amount of dHb in the blood.

With this simple but brilliant method, Pauli and Coryell reported that the magnetic susceptibility of fully oxygenated arterial blood differs by as much as 20% from that of fully deoxygenated venous blood. In fact, oxygenated blood is diamagnetic, minimally affecting the magnetic field just like the water and most of the macromolecules of the tissues, while deoxygenated blood is paramagnetic, producing a clearly measurable, additive magnetic field. The physical-chemical explanation of this behavior is straightforward: hemoglobin consists of two pairs of polypeptide chains (globins), each of which is attached to a complex of protoporphyrin and iron (heme group). In dHb the iron (Fe^{2+}) is in a paramagnetic high-spin state, as four of its six outer electrons are unpaired and act as a paramagnetic agent. When oxygenated, the heme iron changes to a low-spin state by receiving the oxygen's electrons, and Hb becomes diamagnetic.

Studies revealed via NMR that blood T_2 is indeed directly affected by its oxygenation[96], suggesting that T_2 changes alone could be used for functional imaging. In

the meantime, of course, this is a standard method. In a 1.5T clinical magnet, a change in oxygenation from 60% to 70% changes the net intravascular T_2 by 40% in venules and 15% in capillaries. I note here in passing that venules and capillaries have an equal share (each 40%) of any particular voxel's blood volume, but venules are approximately twice as magnetic.

The usual signal increases reported in BOLD fMRI experiments are due to the fact that neural activation induces a regional increase in ***cerebral blood flow (CBF)*** and glucose utilization that is always larger than the ***oxygen consumption rate (CMRO2)***[25,26], since oxygen uptake is diffusion-limited. The net effect of neural excitation is thus a seemingly paradoxical drop in the deoxyhemoglobin concentration, which in turn increases the signal strength.

It is now clear that the BOLD signal depends on the $CMRO_2$ as well as on CBF and cerebral blood volume (CBV), thereby representing a complex response controlled by several parameters[76]. Despite this complexity, much progress has been made toward quantitatively elucidating various aspects of the BOLD signal and the way it relates to the hemodynamic and metabolic changes occurring in response to changes in neuronal activity[54,65].

Spatial Specificity

The primary biological factor determining the specificity of the fMRI signal is the density and architecture of the brain's microvasculature. Intracortical vessels vary in their degree of cortical penetration, ranging from those having a short course, i.e. branching close to the pial surface, to those penetrating the entire width of the cortical sheet and covering a large territory. Their diameter ranges from 20µm to 250µm, and their branching pattern depends on the cortical layer[20]. Successive branching of arteries ultimately creates the capillary bed, a network of capillaries whose thin walls and huge combined surface area allows the ready exchange of oxygen, energy substrates and metabolic wastes. The inter-capillary mesh size (ca. 50µm in cortex) is probably dictated by the diffusion coefficient of oxygen. The human brain has no arteriovenous anastomoses[20], i.e. blood vessels that branch and reconnect, so an increase of arterial flow most likely always leads to a commensurate increase in perfusion, the flow of arterial blood into the capillaries, which in turn enhances delivery of oxygen and nutrients in the parenchyma. An increase in neural activity will evidently result in oxygenation changes in all vessels.

A recent study has also provided the first detailed results on the microvascular system of the macaque primate cortex using an array of anatomical techniques that included corrosion casts, immunohistochemistry, and cytochrome oxidase (COX) staining[106]. Detailed measurements of regional vascular length density, volume fraction, and surface density revealed a similar vascularization in different visual areas. In the lower cortical layers a positive correlation between the vascular and cell density was found, but this relationship was very weak in the upper layers. Interestingly, the vascular density was instead strongly correlated with the steady-state metabolic demand as measured by COX activity, suggesting that the number of neurons and synapses determines an upper limit to an area's integrative capacity; vascularization actually reflects the neural activity of those subpopulations that represent a "default" mode of brain steady state.

FMRI specificity depends on the extent to which the methodology reflects primarily the oxygenation changes in the capillary bed and the surrounding tissue rather than in large vessels (e.g. 100 µm and larger). A significant contribution of the latter, which depends on the area of cortex activated[99], can generate BOLD contrast downstream of the tissue with high metabolic activity, resulting in a mislocalization of activation patterns and an erroneous estimation of their extent. Unless the draining vein is remote from the site of activation this is a minor problem for many cognitive studies using voxels of several millimeters linear dimension, but it is of critical importance for any fMRI study with high spatial resolution.

Strategies for improving specificity have been convincingly demonstrated, although they have yet to be fully implemented in most neuroscientific applications. For example, the contribution of vessels of different sizes towards the BOLD signal depends on the strength of the magnetic field and the MR-pulse sequence employed[75]. High magnetic fields de-emphasize the contribution of large vessels and increase the specificity of the fMRI signal. The reasons for the field benefit are twofold. First, local field inhomogeneities are less forgiving at high field: T_2^* relaxation times become shorter as the field strength increases. This short T_2^*

decreases the visibility of signals from larger vessels. Second, extravascular BOLD increases with field strength more rapidly for small vessels than it does for large vessels. This means that the higher the field the more signal is obtained proportionately from the capillary bed and the parenchyma, which is the actual site of activation. The effects of field strength on specificity have been convincingly demonstrated in animal studies, in which precise cortical maps of columnar organization could be obtained[101].

For any given field strength, signal specificity can also be increased by using pulse sequences that are less sensitive to signals from within and around large vessels. The GE-EPI used by the vast majority of cognitive studies is sensitive to (almost) all vessel sizes[76,107]. In contrast, SE-EPI favors signals from small vessels and parenchyma[95], especially at high field when the signal from venous blood becomes very small.

MRI signal losses can originate from static field inhomogeneities like local variations in field near a large vessel, which can be effectively recovered by spin-echo methods, where an RF pulse refocuses the spins that have previously dephased. Signal loss due to dynamic processes, on the other hand, cannot be refocused. This occurs when spins diffuse in a local field gradient (for instance the field gradient produced by a capillary); because of their displacement, they experience a different field before and after the refocusing pulse, resulting in incomplete refocusing.

This recovery of the MRI signal from static inhomogeneities (near large vessels) accomplished by SE-EPI weights the extravascular contribution toward the microvasculature[107]. Last but not least, because signal changes in SE-EPI originate from the average water diffusion, they show apparent T_2, i.e. water diffusion sensitive transverse relaxation, rather than T_2* dependency, and are therefore less affected by intravascular effects[10,76,107]. Two drawbacks of SE-EPI, however, are decreased sensitivity and imaging speed compared with GE-EPI.

Other fMRI methods that are more specific to capillary signal than GE-BOLD are CBV and CBF methods (e.g. [19,111]). In CBV methods T_2^* of blood is reduced by the injection of iron-containing contrast agent, which eliminates all signal from large and medium-sized vessels. In CBF methods the arterial blood is tagged. After an appropriate waiting period the tagged blood arrives in the capillary bed, so if the proper waiting period is chosen, most of the signal will be arising from the capillary bed.

Spatial Resolution

The spatial resolution of MRI can be reliably determined by calculating the ***point spread function (PSF)*** of the imaging method, which is a collective measure of all factors contributing to image blurring, including intrinsic resolution of the imaging system and any necessary spatial smoothing during or following the imaging procedure. The PSF of an imaging method is determined by having a delta function (i.e. a point source with very high intensity) as input and by determining the width of the resulting spot in the final image. When this concept is applied to the transfer function of the whole fMRI procedure, a point source of 100% contrast is assumed as visual input. The size of the activation is then determined by the neural and vascular transfer function, i.e. the representation of the point source on, say, the primary visual cortex, by imaging factors, i.e. resolution, blurring and post-processing/smoothing, and by neurovascular factors, i.e. vascular smearing and the spatial extent of the hemodynamic response.

Brian Wandell and colleagues were the first to quantify the spatial specificity of the GE BOLD response by estimating its PSF with an elegant paradigm that exploits the retinotopic organization of the primary visual cortex[24]. They found that at 1.5T the width of the BOLD PSF at half its maximal height (i.e. full-width-half-maximum or FWHM) is 3.5 mm. Similar values, 3.9 mm for GE-BOLD and 3.4 mm for SE-BOLD, have been reported at 3T[78]. Predictably, the PSF of GE-BOLD is narrower at 7T, and it can be as small as 2 mm when signals from macrovessels are masked out[87]. Methods such as SE-BOLD, CBV imaging at high fields, and CBF fMRI, which stress oxygenation changes in the capillary bed and parenchyma, further reduce PSF width to 1 mm or less[101]. It should be noted that such measurements only set an upper bound for the width of PSF, because it may also be limited by factors unrelated to imaging, such as organization of cortex or subject behavior. In the visual system, for instance, the PSF will necessarily be affected by eye movements, as well as by intracortical connectivity patterns (e.g. horizontal

connections in early visual cortices) that may spread local activation horizontally[34].

Alternatively to PSF estimation, the limits of the fMRI spatial resolution can be assessed by resolving functional subunits of the brain that have already been shown by invasive methods. The cortical columns of neocortex are prominent examples of such structurally and functionally specialized subunits, whose organization has been studied extensively in the early sensory areas of animals[70]. Not surprisingly, visualization of such structures by means of BOLD, CBF, or CBV imaging has been thought of as the ultimate test for the resolving power of the method and has been attempted ever since the advent of fMRI.

In humans the ocular dominance columns have a mean width of roughly 1 mm[1]. Convincing maps of these columns in normal human subjects were reported only a few years ago using high-field (4T) fMRI that permitted a resolution of 0.47x0.47mm^2 in-plane for a slice thickness of 3mm[16]. However, successful mapping relied on explicit masking out of regions having non-specific large vessels, a procedure that cannot be easily applied in other cortical areas with less well-defined neural and vascular architecture. An alternative to this area-specific macrovessel exclusion is the application of subtraction designs on data collected at very high magnetic field (7T) and by using the SE-BOLD pulse sequence[110]. The combination of field strength and SE-BOLD enabled the unconstrained mapping of human ocular dominance columns with an in-plane spatial resolution of 0.5x0.5mm^2 and a slice thickness of 3mm. In animals, i.e. cats, orientation columns (~1 mm diameter) have also been shown using GE-BOLD, CBV and CBF-based methods (e.g.[19,111]).

Leaving aside certain limitations imposed by the scanner hardware, spatially resolved MRI/fMRI usually suffers from substantial drops in signal-to-noise (SNR) and contrast-to-noise (CNR) ratios that occur as the voxel size decreases. In a single-channel acquisition system small surface coils are often used to substantially improve SNR and increase resolution. Such coils increase SNR both because they can be placed very close to the region of interest and because they reduce the ***sensitive volume***, i.e. the volume from within which signals are received, thus decreasing noise by eliminating signals originating in irrelevant tissues. In animal studies, for instance, resolutions as high as 0.25x0.25mm^2 with a slice thickness of 2mm can be achieved with either GE or SE BOLD using either implantable or surface coils[31]. Yet, in this methodology there is a clear tradeoff between resolution and coverage, the latter being indeed one of the greatest virtues of fMRI and one that cannot be easily given up. But this can be recovered to some extent by parallel imaging.

Temporal Resolution

High spatial resolution is needed to resolve anatomical and functional detail, but fast scanning is needed to achieve a detailed description of successive neural events. Temporal resolution is constrained by both technical and physiological – mostly vascular – factors. Technically, temporal resolution is determined by the sampling rate of the volumes. With conventional acquisition methods the fastest technique with adequate signal-to-noise is single-shot echo planar imaging (EPI)[85], provided that the scanner has strong and fast gradients and that a number of other parameters have been sufficiently optimized to avoid image distortions. The total time needed for the acquisition of an entire image with single-shot EPI can be as short as 40ms. The drawback is that single shot EPI is very sensitive to field inhomogeneities and other artifacts (e.g. T2* blurring). Many of the problems of single-shot EPI can be overcome by using multi-shot (segmented) EPI, which collects data over multiple excitations (shots), although this incurs the risk of significant motion artifact. Currently, using BOLD fMRI with segmented GE-EPI one can collect single slices at a sampling rate of less than 100ms, and volumes of multiple slices at a sampling rate of 1-3 seconds. High sampling rates (e.g. 100 ms or less), however, require special caution to avoid activation-independent signal increases, e.g. inflow effects[21].

Developments and Perspectives

Temporal resolution, as well as SNR and CNR problems in spatially resolved imaging can be dealt with to some extent by using multiple MR-signal acquisition channels, each collecting data from a different small RF coil[47,109]. Parallel imaging with such coil arrays can tremendously improve the nominal resolution of MRI and fMRI, in particular if superconducting (and hence very low noise) coils are used. In fact, within the last 8 years, parallel

imaging methods have become commercially available and are now in broad clinical use.

Parallel MRI (pMRI) works by taking advantage of the spatial sensitivity information inherent in an array of multiple receiver surface coils to speed up the time-consuming spatial encoding normally performed by switching magnetic field gradients.

In the MRI introduction above I briefly indicated that spatial localization in MRI is achieved by using smaller magnetic field gradients that are superimposed on the homogenous magnetic field of the scanner. This strategy exploits the Larmor relationship and encodes spatial information in one direction (e.g. x or ***readout*** direction) in terms of frequency. The usual two-dimensional image is obtained by encoding the other direction (e.g. y or ***phase-encoding*** direction) into the phase of MR signals. Phase- and frequency-encoding directions are perpendicular to each other. While the phase-encoding gradient (PEG) is on, the Larmor frequency becomes linearly proportional to the position along the phase-encoding direction. The phase shift that accumulates by the time the PEG is turned off characterizes each "line" (or row) of the two dimensional image. Accordingly, in a MR image of 128 lines - each 128 voxels long - 128 acquisitions will be required to obtain the complete image. In contrast, with pMRI only a fraction of the phase-encoding steps have to be acquired, resulting in substantially faster image acquisition yet still maintaining full spatial resolution and image contrast.

This decreased acquisition time can obviously be used to improve spatial resolution as well. In addition, pMRI diminishes susceptibility-caused artifacts by reducing the echo train length of single- and multi-shot pulse sequences. Currently, the best known pMRI methods are the so-called ***simultaneous acquisition of spatial harmonics (SMASH)***[89], ***sensitivity encoding (SENSE)***[81], and ***generalized autocalibrating partially parallel acquisitions (GRAPPA*** [35]. For an overview on the advantages and disadvantages of these methods see the review by Blaimer and colleagues[9].

Cognitive and Neural Sciences

On Pure Insertion

Serial subtraction designs rely strictly on ***pure insertion,*** a concept introduced in the context of reaction times (RT). In the 1960s, the work of Donders[18] had proposed that the time between stimulus and response is occupied by a train of successive processes, or stages, each component of which begins only when the preceding one has ended. For example, the visual search for an item defined by the conjunction of two or more stimulus dimensions (e.g. shape and color) is linearly (additively) related to the number of distractors in the visual field [98]. Empirical demonstrations of similar additive relationships between increments in cognitive load and reaction times were later the basis of Sternberg's proposal [93]. Sternberg improved and extended Donders' method to better study various stages of information processing. The main feature of his ***additive-factor*** method was the search for non-interacting effects of experimental factors on mean RT. He suggested that stage durations may be additive without being stochastically independent, and that the effect of a new experimental factor can be localized among a set of already established stages. In other words, according to this pure insertion hypothesis, a single cognitive process can be inserted into a task without affecting the remainder. This assumption is the basis of a large number of experimental designs and analysis methods in cognitive fMRI.

But the idea of pure insertion in the context of brain activation studies is actually misleading and all too often simply not tenable. Even if an experimental design could satisfy this assumption at the cognitive level, the assumption would be condemned to fail utterly at the level of its neuronal instantiation due to the highly non-linear nature of most brain processes[2]. This fact was elegantly demonstrated by Karl Friston and colleagues[28] in their critical assessment of cognitive subtraction as a conceptual framework in brain activation studies.

Neurotransmission and Neuromodulation

Sensory information reaches cortex via fast, mostly glutamatergic or aspartergic synapses, typically producing direct excitatory effects on the postsynaptic neurons via the AMPA and NMDA receptors. The dynamics of activation are strongly affected by recurrent inhibition mediated by GABAergic interneurons. Together, the glutamatergic and GABAergic neurons are responsible for a major part of neurotransmission, which in turns affects the regional cerebral blood flow (CBF). Yet, CBF is also considerably affected by the overall

regulation of cortical dynamics and cell excitability mediated by a number of other neurochemicals, including acetylcholine, norepinephrine, serotonin, dopamine, and various peptides. Although such chemicals were initially defined as classical neurotransmitters in peripheral systems, in cortex they appear to have an important neuromodulatory role. Neurotransmission and neuromodulation are often discriminated on the basis of the activated receptors, with neurotransmitters targeting receptors that are coupled directly to ion channels and neuromodulation affecting receptors coupled to channels via second messenger pathways.

Neuromodulatory innervation originates from various nuclei in the brainstem and basal forebrain and spreads out in a rather diffuse fashion to broad cortical regions[41]. Well studied examples include the noradrenergic ascending system primarily originating in the locus ceruleus (LC), the serotonergic system in nuclei near the midline and the raphe regions of the pons and upper brainstem, the cholinergic system innervating neocortex from the nucleus basalis of Meynert, and the dopaminergic system from the ventral tegmental area (VTA).

In relation to neurovascular coupling, it is important to note that neurotransmission and neuromodulation may often involve different types of interneuronal communication with potentially different spatial specificity and spatiotemporal resolution. Neuromodulation is slow and diffuse, and while it may be induced by sensory stimulation, it is not necessarily stimulus-specific[46].

The lack of strict specificity is also evident in the different types of interneuronal communication that characterize neuromodulation. Many axons of the neuromodulatory nuclei, which typically run long distances through various cortical structures, have certain characteristic ***non-junctional varicosities*** with high densities of small vesicles and absence of synaptic specializations (for a review see[112]). Such varicosities are often located far from any recognizable postsynaptic density. In fact, their serial reconstruction of processes originating in noradrenergic, serotonergic, cholinergic, and dopaminergic nuclei has demonstrated that about 80% of their varicosities do not really match the local postsynaptic densities. It thus appears that there exists a frequent spatial uncoupling between release sites for transmitters and their respective receptors, implying that the transmitter may in principle be poured out in the extracellular space and affect tissue volumes containing relevant receptors over distances much larger than those of the typical synaptic cleft.

On the basis of such observations, two different communication frames have been suggested: ***wiring*** and ***volume transmission***[3]. Wiring transmission implies the existence of specialized communication channels within the neuronal and/or glia cell network, and includes the well-studied synaptic transmission and gap junctions. Volume transmission, on the other hand, is characterized by signal diffusion in a three-dimensional fashion within the brain's extracellular fluid. While such nonjunctional volume transmission is the rule in the peripheral autonomic nervous system, it has also been proposed for the CNS[104]. In the cerebral cortex of monkeys, for example, acetylcholine can reach both pyramidal and nonpyramidal neurons via volume transmission; Cortical noradrenaline innervation is mostly nonjunctional, and the innervation of the forebrain by the dorsal and median raphe nuclei is characterized by spaced varicosities distributed across all areas of the cerebral cortex[45]. The activity of the diffuse ascending systems may thus influence the activation level of large cell populations, and it may do so in a manner less specific to the function in question.

Neural Signals

In order to understand the relationship between the BOLD signal and its underlying neural events it is necessary to comprehend the nature of the neurophysiological signals commonly reported in animal studies, as these are the telltale signs of the underlying neuronal processes (see also reviews[62,63,65]). Physiological studies at the systems and behavioral level in anesthetized or conscious animals typically report extracellular recordings. While the mechanisms at work during the monitoring of transmembrane electrical events with intracellularly placed electrodes are reasonably well understood, the interpretation of different types of extracellular recordings, in particular those reporting on the activity of neural masses, proved to be difficult and it still requires discussion.

Signals Spread in the Extracellular Microenvironment, Which Acts As a Volume Conductor

Neurons are considered to be embedded in an extracellular medium that acts as a ***volume conductor***[66] (for a detailed review on field potentials see[27]; for background in biophysics see textbooks[4,49]). The extracellular microenvironment consists of narrow gaps between cellular processes an average of about 200 Å wide. These spaces form a complex three-dimensional mosaic filled with extracellular fluid, and they account for about 12 to 25% of the brain's volume. Currents and ions spread in this space, and as theoretical reasoning suggests, spread mostly in the extracellular fluid between the cells, but not through them[83]. Hence, the resistance depends on the spatial layout of neurons and glia, resulting in an intricately shaped conductive medium that, in principle, can carry electrical signals over large distances. Confirmation comes from direct measurements of current flow and studies of the diffusion of ions in this microenvironment[42,72,82,102,103]. Given these intricate properties of the extracellular medium it is important to know how this medium conducts the variety of signals generated by subthreshold and spiking activity.

The Volume Conductor Is Quasi-Static, Ohmic and Tangentially Isotropic

Within the physiological frequency range (0 to about 5 kHz), the inductive, magnetic, and propagative (wave) effects of the bioelectrical signals in the extra-cellular space can be neglected[67,83], permitting the description of a current electrode as a simple static point source. Moreover, any description of the volume conductor is further simplified by the fact that the propagation of signals is independent of their frequency[64]. For many years the volume conductor has been described as having a capacitive and anisotropic nature, implying a frequency- and direction-dependent signal propagation (e.g. see review[65]). Yet recent intracranial measurements using a novel variant of the four-point technique[86] showed that tissue impedance is actually frequency-independent, allowing the description of cortex as an ohmic resistor. As such, the tissue can be described by its specific electrical resistance (or resistivity). Finally, the resistive properties of the gray matter are largely isotropic, i.e. its resistivity is the same along each direction[64]. These results have important implications for the origin and spatial summation of different types of neural signals (see below).

Dipoles and Dipole-Layers in the Volume Conductor

What do extracellularly placed electrodes actually measure? When a neuron discharges, it undergoes an increase in conductivity over the excitable membrane regions, i.e. usually at the axon hillock and/or soma. A current flowing into the cell across the regionally increased conductance will flow along the core of the cell, and then exit at various regions of adjacent, inactive membrane to ultimately return to the site of current entry by way of diverse paths through the volume conductor. The active regions of the membrane at any given time point are considered to act as a current ***sink***, while the inactive ones as a ***source*** for the active regions. During the generation of the action potential the neuron can be considered an ***electric dipole*** as the dendrites are positive with respect to the soma. The aforementioned non-zero resistivity of the volume conductor is the reason that the current flow in the extracellular fluid during the activity of neurons generates measurable gradients of potential.

These ***extracellular field potentials (EFP)*** add up linearly and algebraically throughout the volume conductor (the principle of electric superposition), representing the weighted sum of all sinks and sources along multiple cells. The superposition principle sets some constraints in the interpretation of the ***mean extracellular potential (mEFP)*** commonly measured with electrodes. Specifically, the mEFP critically depends on the local geometrical arrangements of neurons. For cells with diametrically opposite orientations, currents of equal magnitude but opposite polarity will generate potentials that tend to cancel each other. As a result, information is potentially lost that cannot be recovered without additional knowledge (e.g. anatomical or intracellularly obtained single-unit data). For certain geometrical arrangements, the way the current flows and the position of sinks and sources along the membranes can be calculated. For others they cannot.

Open, Closed and Open-Closed Fields

Three arrangements produce characteristic mEFP: the ***open***, the ***closed***, and the ***open-closed fields***. The first is encountered when the neurons are organized in a laminar array, with their dendrites facing in one direction and the

somata in the other; typical examples of open field are the neocortex, the cerebellum and the hippocampus. Simultaneous activation of the dendrites of neurons in this arrangement generates strong dipole layers whose field potentials are easily captured by electrodes. The second arrangement produces dipoles with spherical symmetry; the polarity of a measurement within the sphere depends on its location within the spherical dipole, while measurements from outside would record zero potential. Lastly, the third arrangement yields a mixture, whereby measurements within the spherical dipole sense combination of the two fields, while those outside the sphere would simply record changes in the open field component.

Single and Multiple Unit Activity vs. Local Field Potentials

When a microelectrode with a small tip is placed close to the soma or axon of a neuron, then the measured mEFP directly reports the spike traffic of that neuron and frequently that of its immediate neighbors as well. The recordings then reflect ***single unit activity (SUA).*** Tetrodes placed close (within 50 μm) to pyramidal neurons in hippocampus provide accurate information on a number of their parameters such as latency, amplitude and shape of action potentials, as has been demonstrated by means of simultaneous intracellular recordings[40,43]. Single spike monitoring has the best possible spatial and temporal resolution but it provides information mainly on single receptive fields, with no access to subthreshold integrative processes or the associational operations taking place at a given site. Moreover, it is biased toward certain cell types (cf.[94]) and sizes[97]. The measured spikes mostly represent only very small neural populations of large cells, which in cortex are by and large the principal cells (e.g. pyramidal cells in cerebral cortex and Purkinje neurons in cerebellar cortex). Recording from interneurons (e.g. inhibitory cells) is often very difficult both because of their size and because their response is often found to be uncorrelated to the stimulus or behavior state of the animal.

Nonetheless, more than SUA can be measured with microelectrodes. In fact, two different signal types can be easily extracted from the mEFP by using traditional Fourier band separation or the wavelet approach. A high-pass filter cutoff of approximately 1000Hz can be used to obtain ***multiple-unit spiking activity (MUA)***[29], and a low-pass filter cutoff of ca. 300Hz to obtain the so-called ***local field potentials (LFPs).*** MUA has been often calculated by using lower frequency cutoffs (300-800Hz); yet lower cutoffs make far-field potentials noticeable and may occasionally (e.g. by averaging) lead in erroneous MUA interpretations[59]. A large number of experiments have presented data indicating that such a band separation does indeed underlie different neural events. MUA-range activity reflects the variations in the magnitude of extracellular spike potentials. LFPs, on the other hand, represent mostly slow events reflecting cooperative activity in neural populations[62,63,65].

New insights into the generation of LFPs, as well as into intracortical processing in general, have come from the study of inhibitory networks in hippocampus[14,53,56]. These studies provided evidence of the existence of other types of slow activity unrelated to synaptic events, including voltage-dependent membrane oscillations (e.g.[52]) and spike afterpotentials. To be more specific, the soma-dendritic spikes in the neurons of the central nervous system are generally followed by afterpotentials, a brief delayed depolarization, the ***afterdepolarization***, and a longer lasting ***afterhyperpolarization***, which are thought to play an important role in the control of excitation-to-frequency transduction (e.g.[32,37,39]). Afterpotentials, which were shown to be generated by calcium-activated potassium currents (e.g.[15,39,44,55,105]) have a duration on the order of 10s of milliseconds and most likely contribute to the generation of the LFP signals[12,13]. The delta waves of the EEG signal, for example, are not necessarily a result of synaptic activity, but rather reflect the summation of long-lasting afterhyperpolarizations of layer V pyramidal neurons; the suppression of delta waves during neocortical arousal is mainly due to blockade of this hyperpolarization by cholinergic input.

Band Limited Power (BLP) Signals in the LFP Range

Traditionally, low-frequency signal modulations are classified in a number of specific frequency bands initially introduced in the EEG literature (e.g.[22,23,80]). Rhythmic EEG is subdivided into frequency bands known as ***delta*** (δ, 0-4Hz), ***theta*** (θ, 4-8Hz), alpha (α, 8-12Hz), ***beta*** (β, 12-24Hz), and ***gamma*** (γ, 24-40/80Hz) which are typically characterized by different amplitudes[6,61,90,91].

This classification was based on the strong correlation of each band with a distinct behavioral state. The oscillatory activity in these bands is associated with the thalamocortical loops and is modulated by the ascending network system and basal forebrain[90,92]. But rhythmic activity related to some of the EEG frequency bands has also been reported for the spiking principal neurons. Many pyramidal neurons in layer 5 of the neocortex show prolonged, 5- to 12-Hertz rhythmic firing patterns due to intrinsic membrane properties such as sodium conductance, which is essential for rhythmicity, and calcium-dependent conductance, which strongly modifies it[88]. Although synaptic networks of intrinsically rhythmic neurons may still be the origin of the synchronized cortical oscillations, spiking activity in this case will be tightly correlated with the LFPs and will contribute to the modulation of their amplitude.

The definition of the above bands is empirical, and often the range of a particular band is determined arbitrarily, varying, in the case of the gamma band, for example, from 20-50, 20-70, 24-60, or 24-90Hz. An alternative band separation is that based on information theory. Recently the information carried by individual BLP in the LFP or MUA range was calculated in extracellular recordings during the presentation of movies with natural images[7]. The most informative LFP frequency ranges were ***1-8Hz*** and ***60-100Hz***. LFPs in the range of 20-60Hz carried very little information about the stimulus, although they shared strong trial-to-trial correlations, indicating that they might be influenced by a common source, such as diffuse neuromodulatory input. The upper range of the latter band is may often have transition characteristics between the two nearby regions. LFPs in the range of ***12-40Hz*** are distinct and most likely are the best reflection of neuromodulatory input.

Spike power, on the other hand, was informative only at frequencies ***below 12 Hz*** (frequency of bursts). Positive signal correlations were found between LFPs (60-100Hz) and spikes, as well as between signals within this LFP range, suggesting that the 60-100Hz range of LFPs and the spikes might be generated within the same network.

Spatial Summation of Neuronal Signals

The summation range for the fast MUA has been studied by a number of investigators. Electrodes with exposed tips of approximately 100μm (impedance from 40-120kΩ), for example, were estimated to record from a sphere with a radius of 50-350μm[33,36,60], whereby the activity from each point within the sphere is weighted by a factor depending on the distance of the point from the tip of the electrode [71].

LFPs reflect a weighted average of synchronized dendro-somatic components of the synaptic signals of a neural population within 0.5-3 millimeters of the electrode tip[51,68]. The upper limits of the spatial extent of LFP summation were indirectly calculated by computing the phase coherence of LFPs as a function of inter-electrode distance in experiments with simultaneous multiple-electrode recordings[50].

Recently the spatial summation of different BLPs in the LFP range was estimated by ***reverse correlation*** and ***coherence analysis***. Reverse correlation indicated that the site-RF sizes (square root of the area) are about 6.3 mm (delta-theta), 4.2 mm (20-60Hz), 2.3 mm (gamma), 1.9 mm (MUA), and 1.5 mm (SUA). The half-maximum of coherence-to-distance functions, on the other hand, show a coupling region of 2.9mm (2-8Hz), 2.38mm (8-15Hz), 1.94mm (20-60Hz), and 1.48mm for MUA[30]. These findings suggest that the spatial summation is in the range of a typical voxel size in high resolution imaging for both the LFP band as well as the MUA bands. The stronger coupling of different bands of LFP to BOLD can therefore not be explained by a difference in spatial summation.

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CNS 2013 Press Release: Memory, the Adolescent Brain, and Lying: Understanding the Limits of Neuroscientific Evidence in the Law

April 16, 2013

April 16, 2013 – San Francisco – Brain scans are increasingly able to reveal whether or not you believe you remember some person or event in your life. In a new study presented at a cognitive neuroscience meeting today, researchers used fMRI brain scans to detect whether a person recognized scenes from their own lives, as captured in some 45,000 images by digital cameras. The study is seeking to test the capabilities and limits of brain-based technology for detecting memories, a technique being considered for use in legal settings.

"The advancement and falling costs of fMRI, EEG, and other techniques will one day make it more practical for this type of evidence to show up in court," says Francis Shen of the University of Minnesota Law School, who is chairing a session on neuroscience and the law at a meeting of the Cognitive Neuroscience Society (CNS) in San Francisco this week. "But technological advancement on its own doesn't necessarily lead to use in the law." But as the technology has advanced and as the legal system desires to use more empirical evidence, neuroscience and the law are intersecting more often than in previous decades.

In U.S. courts, neuroscientific evidence has been used largely in cases involving brain injury litigation or questions of impaired ability. In some cases outside the United States, however, courts have used brain-based evidence to check whether a person has memories of legally relevant events, such as a crime. New companies also are claiming to use brain scans to detect lies – although judges have not yet admitted this evidence in U.S. courts. These developments have rallied some in the neuroscience community to take a critical look at the promise and perils of such technology in addressing legal questions – working in partnership with legal scholars through efforts such as the MacArthur Foundation Research Network on Law and Neuroscience.

Recognizing your own memories

What inspired Anthony Wagner, a cognitive neuroscientist at Stanford University, to test fMRI uses for memory detection was a case in June 2008 in Mumbai, India, in which a judge cited EEG evidence as indicating that a murder suspect held knowledge about the crime that only the killer could possess. "It appeared that the brain data held considerable sway," says Wagner, who points out that the methods used in that case have not been subject to extensive peer review.

Since then, Wagner and colleagues have conducted a number of experiments to test whether brain scans can be used to discriminate between stimuli that people perceive as old or new, as well as more objectively, whether or not they have previously encountered a particular person, place, or thing. To date, Wagner and colleagues have had success in the lab using fMRI-based analyses to determine whether someone recognizes a person or perceives them as unfamiliar, but not in determining whether in fact they have actually seen them before.

In a new study presented today, his team sought to take the experiments out of the lab and into the real world by outfitting participants with digital cameras around their necks that automatically took photos of the participants' everyday experiences. Over a multi-week period, the cameras yielded 45,000 photos per participant.

Wagner's team then took brief photo sequences of individual events from the participants' lives and showed them to the participants in the fMRI scanner, along with photo sequences from other subjects as the control stimuli. The researchers analyzed their brain patterns to determine whether or not the participants were recognizing the sequences as their own. "We did quite well with most subjects, with a mean accuracy of 91% in discriminating between event sequences that the participant recognized as old and those that the participant perceived as unfamiliar, " Wagner says. "These findings indicate that distributed patterns of brain activity, as measured with fMRI, carry considerable information about an individual's subjective memory experience – that is, whether or not they are remembering the event."

In another new study, Wagner and colleagues tested whether people can "beat the technology" by using countermeasures to alter their brain patterns. Back in the lab, the researchers showed participants individual faces and later asked them whether the faces were old or new. "Halfway through the memory test, we stopped and told them 'What we are actually trying to do is read out from your brain patterns whether or not you are recognizing the face or perceiving it as novel, and we've been successful with other subjects in doing this in the past. Now we want you to try to beat the system by

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altering your neural responses.'" The researchers instructed the participants to think about a familiar person or experience when presented with a new face, and to focus on a novel feature of the face when presented a previously encountered face.

"In the first half of the test, during which participants were just making memory decisions, we were well above chance in decoding from brain patterns whether they recognized face or perceived it as novel. However, in the second half of the test, we were unable to classify whether or not they recognized the face nor whether the face was objectively old or new," Wagner says. Within a forensic setting, Wagner says, it is conceivable that a suspect could use such measures to try to mask the brain patterns associated with memory.

Wagner says that his work to date suggests that the technology may have some utility in reading out brain patterns in cooperative individuals but that the uses are much more uncertain with uncooperative individuals. However, Wagner stresses that the method currently does not distinguish well between whether a person's memory reflects true or false recognition. He says that it is premature to consider such evidence in the courts because many additional factors await future testing, including the effects of stress, practice, and time between the experience and the memory test.

Overgeneralizing the adolescent brain

A general challenge to the use of neuroscientific evidence in legal settings, Wagner says, is that most studies are at the group rather than the individual level. "The law cares about a particular individual in a particular situation right in front of them," he says, and the science often cannot speak to that specificity.

Shen cites the challenge of making individualized inference from group-based data as one of the major ones facing use of neuroscience evidence in the court. "This issue has come up in the context of juvenile justice, where the adolescent brain development data confirms behavioral data that *on average* 17-year-olds are more impulsive than adults, but does not tell us whether a *particular* 17-year-old, namely the one on trial, was less able to control his/her actions on the day and in the manner in question," he says.

Indeed, B.J. Casey of the Weill Medical College of Cornell University says that too often we overgeneralize the lack of self control among adolescents. Although adolescents do show poor self control as a group, some situations and individuals are more prone to this breakdown than others.

"It is not that teens can't make decisions, they can and they can do so efficiently," Casey says. "It is when they must make decisions in the heat of the moment – in presence of potential or perceived threats, among peers – that the court should consider diminished responsibility of teens while still holding them accountable for their behavior." Research suggests that this diminished ability is due to the immature development of circuitry involved in processing of negative or positive cues in the environment in the subcortical limbic regions and then in regulating responses to those cues in the prefrontal cortex.

The body of research to date is at the group-level, however, and is not yet able to comment on the neurobiological maturity of an individual adolescent. To help provide more guidance on this issue in legal settings, Casey and colleagues are working alongside legal scholars on a developmental imaging study, funded by the MacArthur Foundation, that is examining behaviors relevant to juvenile criminal behavior, including impulsivity and peer influence.

Making real-world connections

The same type of work – to connect brain imaging to particular behaviors in the real-world – is ongoing in a number of other areas, including fMRI-based lie detection and linking negligence to specific mental states. "It's a big leap to go from a laboratory setting, in which impulse control may be measured by one's ability to not press a button in response to a stimulus, to the real-world, where the question is whether someone had requisite self-control not to tie up an innocent person and throw them off a bridge." Shen says. "I don't see neuroscience solving these big problems anytime soon, and so the question for law becomes: What do we do with this uncertainty? I think this is where we're at right now, and where we'll be for some time."

"With a few notable exceptions such as death penalty cases, cases where a juvenile is facing a very stiff sentence, and litigating brain injury claims, 'law and neuroscience' is not familiar to most lawyers," Shen says. "But this might change – and soon." The ongoing work is vital, he says, for laying a foundation for a future that's yet to come, and he hopes that more neuroscientists will increasingly collaborate with legal scholars.

The symposium "Neuroscience and Law: Promise and Perils" takes place on April 16, 2013, at the 20th annual meeting of the Cognitive Neuroscience Society (CNS). More than 1,400 scientists are attending the meeting in San Francisco, CA, from April 13 to April 16, 2013. Follow the meeting on Twitter: @CogNeuroNews #CNS2013

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Media Contact:

Lisa M.P. Munoz, CNS Public Information Officer
703-951-7331
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Searching for Signatures of Brain Maturity: What Are We Searching For?

Leah H. Somerville[1,*]
[1]Department of Psychology and Center for Brain Science, Harvard University, Cambridge, MA 02138, USA
*Correspondence: somerville@fas.harvard.edu
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Evidence of continued neurobiological maturation through adolescence is increasingly invoked in discussions of youth-focused policies. This should motivate neuroscientists to grapple with core issues such as the definition of brain maturation, how to quantify it, and how to precisely translate this knowledge to broader audiences.

The study of brain development encompasses evaluation of the structural, functional, and network-level changes that occur across the lifespan, along with the mechanisms that propel these changes (e.g., hormonal influence, experience, and so on). Over the past two decades, there has been an explosion of evidence revealing that despite being roughly equal in size, the brains of human children, adolescents, and adults differ in complex ways. Questions about the pace, timing, and psychological consequences of human neurodevelopment have thus fascinated basic scientists, clinical and applied scientists, and the general public.

Discussions in legal and policy communities have also begun to incorporate neuroscientific evidence of immaturity into their arguments. Continued neurodevelopment has been cited in developmentally informed legal considerations such as culpability for criminal behavior and determinations of competence for health-related decision making (Steinberg, 2009a). Continued neurodevelopment also implies continuing plasticity, a tenet that supports developmentally timed interventions for health-risk behaviors. It is exciting that basic neuroscience is infiltrating public discourse to guide developmentally informed policies and treatment of youths.

Arguments for (neuro)developmentally informed policy rest on a foundational claim that youths' brains are "still-maturing," implying that they differ in some key way from a mature, adult point of reference. However, the complex nature of neurodevelopment itself poses challenges to establishing a point of reference that would indicate when a brain is mature. To complicate things further, there is little agreement among basic scientists on what properties of a brain should be evaluated when judging whether a brain is mature. This lack of consensus could reflect the fact that most neuroscientists are typically focused on the "journey"—the temporal unfolding of a particular development process—more than when a brain reaches a particular "destination."

The challenge of pinpointing the fuzzy concept of maturity is hardly constrained to neuroscience. There is widespread lack of agreement on the age at which individuals should be considered adults (with the associate rights and protections) based on psychological indicators of maturity as well. However, neuroscientific-based evidence of continued maturity is especially (and perhaps excessively) persuasive in shaping thinking in legal and policy spheres (Steinberg, 2009b). For example, neuroscientific data indicating continued brain maturation through adolescence was cited in a brief for the Supreme Court case *Roper v Simmons*, which categorically overturned the death penalty for juveniles. Because neuroscientific evidence is used to promote developmentally informed policy with increased frequency, it has become important for basic neuroscientists to critically examine the concept of "brain maturity" and to consider ways for basic science to improve its translatability on this issue.

What Properties of a Brain Deem It Mature?

In the neurodevelopmental literature, a given neural measurement is typically interpreted as mature when it matches (to a sufficient degree) an "adult" reference. However, brain maturation is a multilayered process that does not map on to a single developmental timeline. On the gross structural level, the developing brain exhibits reductions in cortical gray matter and increases in the volume and anisotropy of white matter from childhood to adulthood (Giedd et al., 1999). Although the field continues to refine its understanding of the cellular-molecular mechanisms underlying gross changes observable with magnetic resonance imaging (MRI), these changes are broadly thought to reflect synaptic pruning, myelination, and increased connectivity across widely distributed brain circuitry.

Longitudinal studies have been particularly informative in charting trajectories and points of asymptote in neurodevelopment. They show that reductions of cortical gray matter and increases in white matter continue to actively change well into the twenties and that a point of stability emerges earlier in some brain structures than others. Generally, regions of association cortex including the prefrontal cortex show particularly late structural development, whereas subcortical and occipital regions asymptote substantially earlier (Ostby et al., 2009; Tamnes et al., 2010; see Figure 1A). However, structural development continues to progress for a surprisingly long time. One especially large study showed that for several brain regions, structural growth curves had not plateaued even by the age of 30, the oldest age in their sample (Tamnes et al., 2010; see Figure 1B).

Other work focused on structural brain measures through adulthood show progressive volumetric changes from

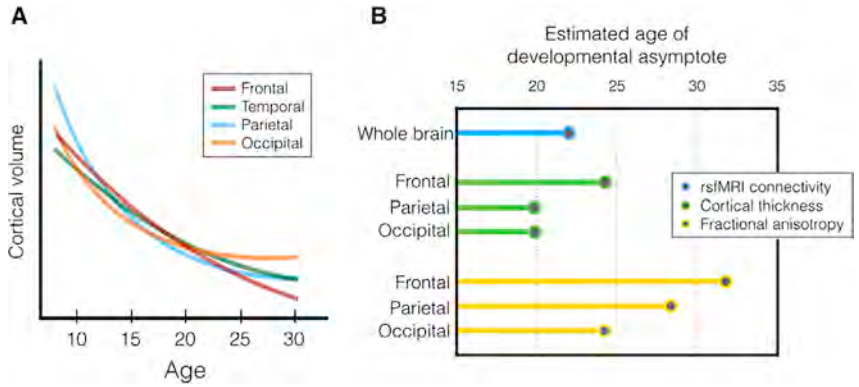

Figure 1. Regional and Methodological Variance in Neurodevelopmental Indices
(A) Trajectories of cortical gray matter volume adjusting for total brain volume. Trajectories are schematized from data reported in Ostby et al. (2009).
(B) Ages of developmental asymptote for connectivity and structural data. Resting-state functional connectivity (rsfMRI) data from Dosenbach et al. (2010) and the other measures reflect data reported in Tamnes et al. (2010). Note that the operationalization of "asymptote" varies by study.

ages 15–90 that never "level off" and instead changed constantly throughout the adult phase of life (Walhovd et al., 2005). Thus, a key challenge to classifying maturity based on structural indices is that it is ambiguous when an adult reference reaches a steady set-point—it depends on the type of anatomical measurement and the lobe or brain region selected. Moreover, it is unclear whether there is even a steady set-point at all.

Another maturing feature of the brain is the intrinsic patterns of connectivity that comprise brain networks. Measures of widespread brain connectivity shift in complex ways from childhood to adulthood, characterized by reductions in local connections and rises in distributed connections. These connectivity-based shifts are thought to reflect a brain that is becoming more efficient in its in-network communication and more integrated in its cross-network communication (Fair et al., 2009).

Dosenbach and colleagues (2010) used data-driven classification algorithms to compute an estimated "brain age" of individual subjects 7 to 30 years of age based on widespread intrinsic connectivity patterns within and between brain networks, measured using resting-state functional connectivity. Their classification algorithms identified adolescence as a period of rapid and widespread increase in connectivity followed by a slowing rate of change until approximately age 22, which was identified mathematically as the point of asymptote. This work suggests that widespread network connectivity measures settle into a fairly consistent reference state in the early 20s. However, these data also illustrate the challenges of applying general patterns of neurodevelopment from group-based to individual inference, as there is substantial variance in brain network connectivity that is unrelated to age. For example, some 8-year-old brains exhibited a greater "maturation index" than some 25 year old brains.

This section has described the neurodevelopmental trends of just two (structure, intrinsic connectivity) of several levels of brain maturation. Other neurodevelopmental processes include neurochemical shifts in neurotransmitter availability and receptor density, brain metabolic efficiency, hormonal change, and excitatory/inhibitory balance. On one hand, there is partial convergence in structural change and intrinsic connectivity, in that the maturational asymptotes for both indices extend well past the age of 18 (the legal definition of adulthood in the United States). On the other hand, there is also strong divergence. One could ascribe maturity to a brain based on network connectivity a decade sooner than based on some structural indices (see Figure 1B). Further, demonstrations of constant change in structure throughout adult life challenge the very notion that the brain reaches a steady adult referent that we can concretely call "mature."

How Does a Mature Brain Function?

How the brain processes information and orchestrates behavior is central to claims about maturity. Children's and adolescents' psychological competencies are changing in a host of functional domains relevant to policy, such as improvements in abstract reasoning and higher-order cognitive skills, and non-linear peaks in reward sensitivity during adolescence. These competencies scaffold on the brain's developing functional networks, evident in studies demonstrating changes in brain-behavior relationships with age.

There has been a recent surge of interest in the brain function of "emerging adults," individuals approximately 18–22 years old who most societies treat as adults but for whom neurobiological maturation is incomplete by almost any metric. Recently, Cohen and colleagues (2016) tested the degree to which the brains of 18–21 year olds functioned more similarly to adolescents or adults while engaging in a regulatory task including threatening cues and threatening contexts. Results showed that in the functioning of key brain areas such as the dorsolateral prefrontal cortex, the 18–21 year olds' brain activity during threat conditions was more similar to a 13–17 year old reference group than a 22–25 year old reference group. These findings provide convergent evidence for continued neurodevelopment during the 18- to 21-year-old window.

Like structural data, functional data can be evaluated relative to an adult reference point. However, developmental changes in brain function can differ from adult brain function in a host of ways that extend beyond whether there is more or less activation in a particular brain region relative to adults. Take for instance neural responses during a complex decision making task. An adolescent group could differ from an adult group in a variety of ways. They could take longer (and require temporally extended neural computations) to arrive at the same choice, they could make a different choice but use the same general neural processes to arrive at that choice, or their decision making could employ an entirely different suite of strategies and neural processes to arrive at either the same or a different choice. Each of these underlying sources of developmental difference could be

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linked to a different neurodevelopmental pattern in functional data.

Pinpointing what neural signals track shifting behavior is a complex and important topic that is addressed elsewhere (Poldrack, 2015). For the current discussion, the key point is that there is no single progression that encompasses functional maturation. Neural activity intensifies and reduces, varies quantitatively and qualitatively, in linear and nonlinear ways that are both linked to—and independent of—behavioral differences across development. Each of these patterns reflects developmental progress, but the wide range of "journeys" prohibits a simple definition of what emerging brain functional maturity looks like.

Multiple Maturities

A key principle that guides determinations about psychological maturity in adolescence and young adulthood is the degree to which contextual factors shape an individual's behavior. For instance, an adolescent and an adult could achieve an identical level of performance on a cognitive task under certain conditions—say, when free of distraction and when the situation has low emotional arousal. However, if the context is shifted slightly by embedding reward cues in the cognitive task, adolescents' performance disproportionally shifts compared to adults (e.g., Somerville et al., 2011). Whereas adolescents might have the baseline *capability* of achieving a certain level of performance, they might not *express* that capability equivalently across situations. Behavioral research has indicated that adolescent regulatory behavior is challenged more than adults in contexts involving emotion, social evaluation, and reward. The contextual dependency of adolescent behavior implies that there is not one threshold of maturity—rather, there are waves of maturity that shape how influential different contexts are on behavioral performance. A prime example of context-sensitive policy is graduated driving laws. They initially constrain new drivers to highly regulated conditions (e.g., during the day, without peers in the car) and slowly broaden the range of driving contexts as new drivers gain experience.

How can neuroscience inform the concept of multiple maturities? As described earlier, different brain regions reach adult-like states at different paces and at different ages. The strong influence of emotional and motivational contexts on adolescent behavior is thought to emerge due to normative, biased circuit-level interactions between motivational and regulatory signaling in the brain (Casey et al., 2016). For instance, neuroimaging evidence has accumulated to suggest that functioning of striatocortical circuitry, which integrates signals of valuation, regulatory demand, and action, is biased in adolescents in contexts in which motivational value is high (Somerville et al., 2011). As such, a relevant marker of a mature brain might actually be a relative imperviousness to context more than any static pattern of neural activation or connectivity.

Narrowing in on Neurobiological Maturity

The work featured in this article highlights the challenges of operationalizing when a brain achieves "maturity." Some neuroscientists may believe that the very notion of defining brain maturity is a misguided objective, as the brain never stops changing across the entire lifespan. However, seeing that neuroscientific claims are highly influential in shaping policy, neuroscientists' voices should guide dialog on when a brain plateaus to an adult-like reference state.

Let's imagine considering a brain mature when *every* index of brain structure, function, and connectivity hits an asymptote. When would an average brain reach this threshold of maturity? From what I've reviewed above, the answer might lie sometime between "the 30s" and "never." This range is remarkably late, given that arguments about reaching maturity tend to focus on the brains and behavioral profiles of individuals in their late teens and early twenties. It is important to acknowledge that claims that the brain reaches maturity earlier (in the early twenties, for instance) are based only on a subset of the available indices of brain maturation.

An open question is whether some indices of brain structure and function should be prioritized over others in conversations about brain maturity. One way to answer this question would be to consider the goals of deeming a brain "mature" from a policy perspective. Brain imaging is primarily being used to corroborate evidence from behavioral science that adolescents (and sometimes young adults) are "on the journey" toward achieving a particular suite of behavioral capabilities. Given that these arguments center on psychological development, perhaps measures of brain function *in relation to the corresponding psychological domains* should be given priority. A focus on brain function would hold an advantage over other measures, because it would allow for estimates to reflect the context dependencies that also characterize adolescents' behavior. However, one consequence of this framework would be the need to abandon the goal of identifying a single age-of-brain maturity. Rather, there would be a suite of maturity points that reflect different neural systems and different associated behaviors. For example, an individual could reach an age of "baseline cognitive maturity"—the capacity to engage in goal-directed behavior under neutral, non-distracted circumstances, substantially earlier than an age of "cognitive-emotional maturity"—the capacity to maintain goal-directed behavior in the face of competing emotional cues.

Concluding Recommendations

It is exciting that dialogue about neuroscience is infiltrating policy considerations for youth. Likewise, neuroscientists can consider how to improve the translatability of their basic research. New large, multimodal brain imaging studies (such as the Adolescent Brain Cognitive Development study http://abcdstudy.org and the Human Connectome Project in Development) will bring forth unprecedented opportunity to pinpoint the timing of healthy brain development. These studies will provide test-beds for establishing intricate models of the pacing and interrelationships between brain structural, functional, and network development across several functional domains. In time, these large datasets could allow for the creation of multimodal "growth curves" which can be linked to behavioral profiles of interest to policy.

What can be done in the meantime? For one, many studies comparing adolescents to young adults frequently use an age of 18 as a cut-point for comparison

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between "adolescents" and "adults," an approach that could obscure or even mask continued developmental change. Researchers could instead avail themselves of the nonlinear and growth curve modeling methods that allow for observation of full trajectories of change. Further, developmental studies frequently truncate "adult" samples at age 22 or even younger—typically too early to document points of asymptote in a particular neural process. Studies that do this might fail to capture the "leveling off" pattern that is thought to characterize mature brain function. Finally, given that behavior arises from complex circuit interactions in the brain, measures of functional brain activity in single brain regions should be supplemented with measures of brain functional connectivity and multimodal methods to identify interrelationships between brain structure, network organization, and function. These approaches will provide a more comprehensive view of the complex suite of mechanisms underlying brain maturation.

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Review

Beyond stereotypes of adolescent risk taking: Placing the adolescent brain in developmental context☆

Daniel Romer[a,*], Valerie F. Reyna[b], Theodore D. Satterthwaite[c]

[a] Annenberg Public Policy Center, University of Pennsylvania, United States
[b] Human Neuroscience Institute, Cornell University, United States
[c] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, United States

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ABSTRACT

Recent neuroscience models of adolescent brain development attribute the morbidity and mortality of this period to structural and functional imbalances between more fully developed limbic regions that subserve reward and emotion as opposed to those that enable cognitive control. We challenge this interpretation of adolescent development by distinguishing risk-taking that peaks during adolescence (sensation seeking and impulsive action) from risk taking that declines monotonically from childhood to adulthood (impulsive choice and other decisions under known risk). Sensation seeking is primarily motivated by exploration of the environment under ambiguous risk contexts, while impulsive action, which is likely to be maladaptive, is more characteristic of a subset of youth with weak control over limbic motivation. Risk taking that declines monotonically from childhood to adulthood occurs primarily under conditions of known risks and reflects increases in executive function as well as aversion to risk based on increases in gist-based reasoning. We propose an alternative Lifespan Wisdom Model that highlights the importance of experience gained through exploration during adolescence. We propose, therefore, that brain models that recognize the adaptive roles that cognition and experience play during adolescence provide a more complete and helpful picture of this period of development.

1. Introduction

Recent theorizing and research regarding the neurodevelopment of the adolescent brain has generated considerable attention in both the popular media and the scientific literature. The most striking generalization stemming from this work is that the adolescent brain does not fully mature until at least age 25, with the implication that adolescent decision-making and judgment is similarly limited up to this age (Casey et al., 2008; Giedd, 2004; Steinberg, 2008). This conclusion rests on research indicating that the myelination and pruning of the prefrontal cortex (PFC) continues into adulthood, well after ventral limbic regions that control motivation and reward have achieved these milestones. As a result, it is proposed that adolescents suffer from a structural as well as functional deficit in the ability of the PFC to exert top-down control over drives that are spurred by the limbic motivational system, leading to less than "rational" behavior during adolescence. The basic dynamics of these neurobiological imbalance models are illustrated in Fig. 1 (Casey et al., 2008), showing that limbic structures are activated in excess of prefrontal cognitive control regions during the adolescent period.

A key feature of such imbalance models is the suggestion that a developmental deficit in PFC cognitive control limits adaptive decision making by adolescents.[1] However, when Giedd et al. (1999) first presented evidence of declining PFC gray matter volume in adolescents, they attributed the phenomenon to the role that experience plays in sculpting the brain during this developmental period. As they put it, the decline in PFC gray matter "may herald a critical stage of development when the environment or activities of the teenager may guide selective elimination during adolescence." (p. 863). In other words, gray matter decline in the PFC could reflect pruning that results from the experience that adolescents gain during this period rather than a direct marker of increasing behavioral control. As Spear (2010) also noted, pruning may

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* Corresponding author.
E-mail address: dan.romer@appc.upenn.edu (D. Romer).

[1] In a recent review of imbalance research, Casey (2015) prefers not to describe imbalance as a "deficit" but rather a "brain that is sculpted by evolutionarily based biological constraints…." Nevertheless, these constraints are seen as contributing to a "200% increase in preventable deaths (accidents, suicide, homicide)…" during adolescence (p. 296–297).

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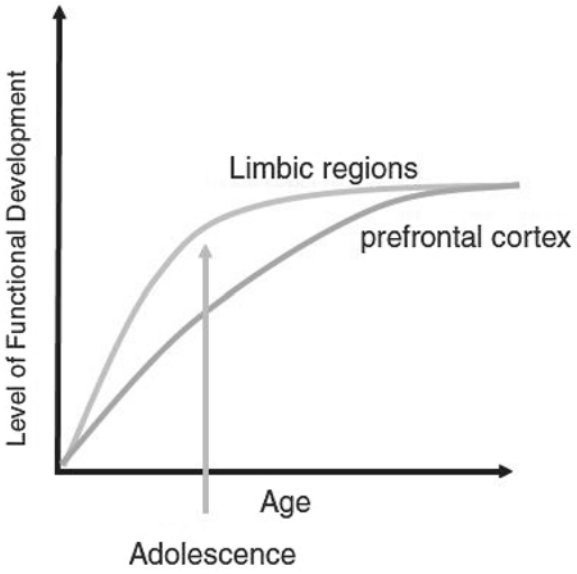

Fig. 1. Casey et al. (2008) model of imbalance between prefrontal versus limbic control over behavior in adolescence.
With permission from Institute of Medicine (2011, p. 38).

be "an example of developmental plasticity whereby the brain is ontogenetically sculpted on the basis of experience to accommodate environmental needs." Needs could vary dramatically across environments and cultures (Mata et al., 2016), potentially resulting in very different patterns of pruning and brain organization during adolescent brain development (Choudhury, 2010). For example, evidence has accumulated to suggest that differences in socioeconomic status, which are correlated with cultural influences, are associated with differences in brain structure (Brito and Noble, 2014; Noble et al., 2015). In particular, Noble et al. (2015) demonstrated that lower socioeconomic status was associated with diminished cortical surface area and reduced hippocampal volume even when controlling for maternal education. Such hippocampal volume reductions have been reported by other studies as well (Hanson et al., 2011; Hueston et al., 2017). Others have observed differences in language-related regions (Piccolo et al., 2016) and modular brain organization (Krishnadas et al., 2013). Future research should unpack influences of education, culture, and income (with concomitant effects on nutrition, access to healthcare, and other factors that may plausibly affect development) on specific aspects of brain development.

Rather than emphasizing the important role of culture and experience in shaping the development of the brain, researchers have instead focused on excess levels of maladaptive risk behavior, such as injury, drug use, pregnancy, and other unhealthy outcomes, as support for imbalance (Dahl, 2004; Steinberg, 2008; Casey, 2015). However, the stereotype of the impulsive, emotional, and distraught adolescent rests much more on the *rise* in adverse outcomes during this age period than on their *overall prevalence* (Institute of Medicine, 2011; Rivers et al., 2008). For the vast majority of adolescents, this period of development passes without substance dependence, sexually transmitted infection, pregnancy, homicide, depression, suicide, or death due to car crashes (Institute of Medicine, 2011; Willoughby et al., 2013). Indeed, the risks of these outcomes are often comorbid with each other (Biglan and Cody, 2003; Kreuger et al., 2002), leaving the average adolescent without great risk of life-altering consequences.

We do not question the reality that the adolescent period entails risk. What we challenge is the interpretation of the brain and behavioral underpinnings of this risk. Research suggests that the brain is structured to enhance development by encouraging movement toward independence and self-sufficiency, a process that supports exploration and learning (Luna and Wright, 2015; Murty et al., 2016; Spear, 2013). Support for this view has been observed in both humans and other animals following the onset of puberty. Nevertheless, a focus on adverse outcomes leaves us with a biased picture that limits our ability to identify adaptive features of adolescent brain development within the context of the entire lifespan. Instead, we argue for a more nuanced interpretation of risk taking and its implications for healthy development. In particular, we outline the evidence regarding the role of sensation seeking, which although it peaks during adolescence does not reflect imbalance, as opposed to forms of impulsivity which either do not peak or only characterize a subset of youth. Our review of research regarding structural development indicates that the relation between brain structure and risk taking has failed to consider the implications of different forms of risk taking. Our analysis suggests that stereotypes of adolescents as particularly susceptible to unhealthy risk taking simplifies how adolescents think about risk and ignores the important role that experience plays in more adaptive forms of risk taking (Reyna et al., 2015a; Romer, 2010). In what follows, we consider what a broader perspective on adolescent brain development would suggest, how that helps to explain the way adolescents make decisions, and how these decisions can be improved.

1.1. The rise in sensation seeking

Consistent with stereotypes of young people, adolescents exhibit heightened attraction to novel and exciting experiences despite their evident risk (Chambers et al., 2003; Romer and Hennessy, 2007; Spear, 2010). This tendency, known as sensation seeking (Zuckerman, 2007), rises rapidly during adolescence. As seen in Fig. 2, a nationally representative U.S. survey of 1800 youth indicates that sensation seeking peaks around age 19 in males and 16 in females. A similar pattern has been observed across a wide range of countries (Duell et al., 2016). This rather striking pattern is regarded as a marker of rising dopaminergic activation during adolescence (Chambers et al., 2003; Wahlstrom et al., 2010) and may reflect activity in the midbrain dopamine pathway ascending from the ventral tegmental region (Ikemoto, 2007; Previc, 2009). This pathway traverses through the ventral striatum before branching into the orbital and ventromedial frontal cortex. These regions are heavily involved in recognition and anticipation of reward (Pagnoni et al., 2002; Schultz et al., 1997) and thus suggest a biological basis for increased attraction to novel and exciting experience during adolescence that declines as the brain transitions to adulthood (see Wahlstrom et al., 2010 for a review of evidence linking a peak in exploratory behavior during adolescence with changes in dopamine expression over the lifespan). A related personality cluster known as the behavioral activation system (BAS) is also believed to be related to

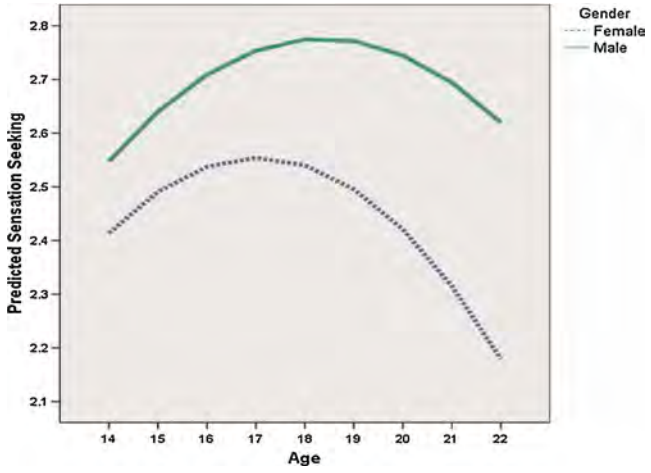

Fig. 2. Trends in sensation seeking by gender in a national U. S. sample.
With permission from Romer (2010).

dopamine function (Carver and White, 1994). One of the indicators of the BAS known as fun seeking is highly related to sensation seeking, while two other related indicators (reward responsiveness and drive) may be more associated with achievement motivations (Romer et al., 2016).

What is often neglected in discussion of imbalance is a rise in dopamine activity in dorsal and medial PFC (Meng et al., 1999; Weickert et al., 2007) fed by another pathway originating primarily in the substantia nigra that ascends through dorsal striatum into dorsal PFC and parietal cortex, regions that control movement and higher order decision making (Ikemoto, 2007; Previc, 2009). Dopamine neurons in this pathway appear to serve more global salience and cognitive processing functions than the ventral route (Bromberg-Martin et al., 2010; Roeper, 2013). This pathway enables the adolescent brain to exert greater attention and other executive functions that are important abilities for reasoning and complex decision-making (Cools et al., 2008; Cools and Robbins, 2004). In particular, dopamine is critical for the maintenance of activity in working memory (WM) (Arnsten et al., 2012; D'Esposito and Postle, 2015), a function centered in frontoparietal cortex that is critical for recruiting experience-based information during decision making (Fuster, 2009; Miller and Cohen, 2001; Shamosh et al., 2008). However, dopamine activation in the dorsal striatum has also been linked to various cognitive functions, including cognitive control and episodic memory (Bäckman et al., 2000; Bäckman et al., 2006; Volkow et al., 1998). Furthermore, as we describe below, both structural and functional dopamine activity in the striatum and PFC declines starting in the third decade of life with associated declines in these cognitive functions. Thus, the rise in dopaminergic activity that may underlie sensation seeking is also accompanied by increased dopaminergic activity in corticostriatal pathways that support the ability to exert control over rewarding experience and to learn from it (Murty et al., 2016; Whalstrom et al., 2010).

1.2. Brain development and adolescent self control

Emphasis on the reward-related functions of dopamine has reinforced a focus on impulsive behavior during adolescence. However, if the adolescent brain undergoes development in both ventral motivational and dorsal cognitive capacities, then the hypothesis of structural and functional imbalance as a normative developmental pattern needs reconsideration. Indeed, contrary to structural imbalance models of brain development, individual differences in sensation seeking (and associated risk taking) have been found to be *positively* correlated with WM and other indicators of executive function (Raine et al., 2002; Romer et al., 2011; Zuckerman, 2007). In one longitudinal study (Romer et al., 2011), individual differences in WM predicted subsequent levels of sensation seeking *even after controlling for age*, suggesting that sensation-based risk taking rises in concert with executive function. Indeed, executive function rises rapidly during adolescence (as does sensation seeking) and asymptotes well before age 25 (Gur et al., 2012; Luciana et al., 2005; Luna et al., 2004; Williams et al., 1999). Thus, the rise in dopamine expression during adolescence may play a role in both sensation seeking and executive function.

Recent models of dopamine expression in mice and rats suggest that dopamine neurons become active in ventral and dorsal striatum prior to their emergence in medial PFC (mPFC) (Naniex et al., 2012; Reynolds et al., 2017). Indeed, dopamine pathways between orbitofrontal PFC and the striatum are in place prior to adolescence in humans (Fareri et al., 2015). The growth of dopaminergic connections between the striatum and mPFC is associated with improvements in cognitive functions related to value learning (Naniex et al., 2012; Reynolds et al., 2017). However, these gaps are eliminated by early adulthood, perhaps mirroring what happens in humans. As dopamine function in the mPFC grows during adolescence, there is also evidence that activation in the dorsal striatum is weaker than in the ventral region, a pattern that may have the adaptive function of enhancing exploration and action-outcome learning (Matthews et al., 2013). Nevertheless, many important cognitive functions that are subserved by the dorsal striatum and its connection with ventral PFC are in place prior to adolescence, and consistent with the development of cognitive control in humans, dopaminergic control over cognitive ability centered in the mPFC appears to be available by early adulthood.

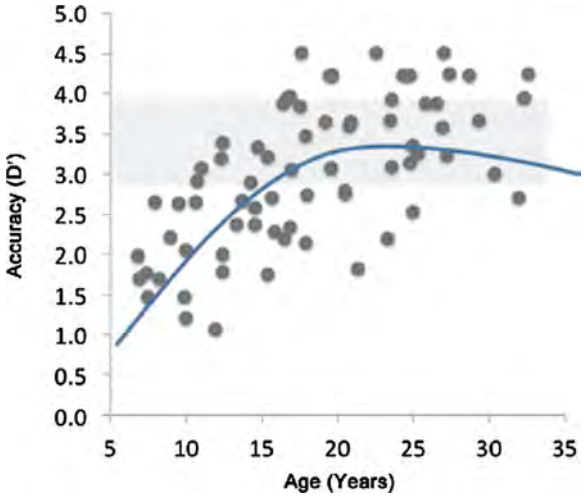

Fig. 3. Data illustrating development of cognitive control during adolescence and early adulthood.
With permission from Casey and Caudle (2013).

In view of the rise in both limbic and prefrontal dopamine expression during adolescence, the generalization that adolescents lack cognitive control relative to limbic activation may have been overstated, a conclusion also reached by Crone and Dahl (2012). Following their review of imaging studies of functional brain development, they found no pattern of brain activation that consistently distinguished adolescent from adult performance in cognitive control tasks: Some cognitive control tasks elicited higher activation in adolescents versus adults, whereas other tasks elicited lower activation. As seen in Fig. 3, by ages 16 and 17, the variability in executive control as assessed in a go-no task is already so large that many adolescents in that age range perform at a level that is equal to that of adults. Although early adolescents perform below the average level of adults in go/no-go and similar tasks, most late adolescents are either equal to or better than the average adult (Williams et al., 1999).

Similarly, in one of the largest imaging studies of executive function in youth ages 8–22, Satterthwaite et al. (2013a) found that differences attributable to age were much smaller than individual differences in performance on an N-back WM task (see Fig. 4). Although WM improved with age, individual differences were large, with many late adolescents exhibiting better WM performance than the average young adult. Furthermore, brain scans demonstrated that WM performance was correlated with enhanced activation in PFC executive regions along with reduced activation of the default mode, which includes limbic cortex (Buckner et al., 2008; Raichle and Gusnard, 2005). Thus, while WM and executive function do improve with age in the aggregate, individual differences are large, such that many late adolescents are as capable as adults at recruiting performance-relevant activation of the executive system and deactivation of default mode regions.

1.3. Sensation seeking vs. impulsivity in adolescent development

A major contention of imbalance models is that adolescents are more subject to poor impulse control than either children or adults. For example, Casey (2015, page 299) notes that imbalance is "presumably not observed in childhood because there is a relative lack of maturity across and between regions within the (corticosubcortical) circuit, and in adults, there is a relative maturity of the underlying neurocircuitry."

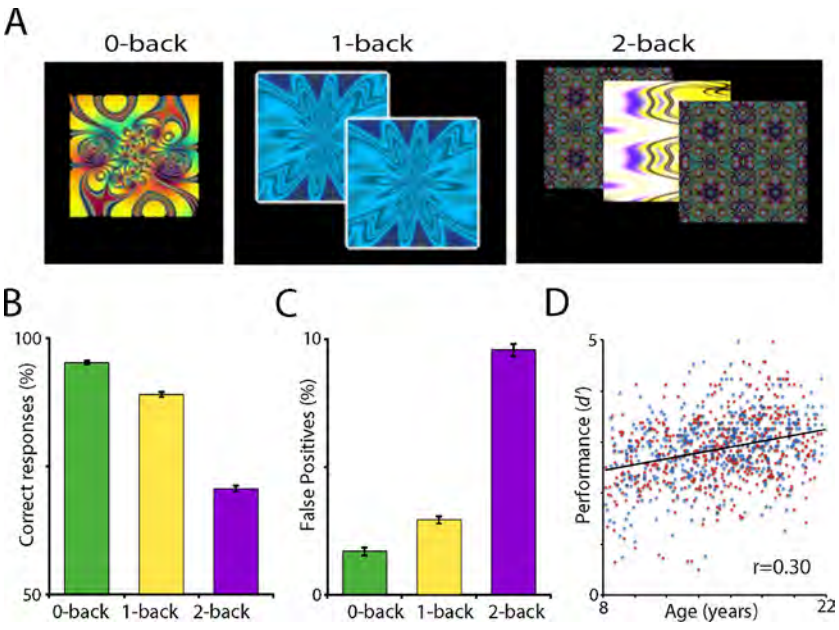

Fig. 4. Data from Satterthwaite et al. (2013 with permission) illustrating the rise in WM ability from ages 8 to 22 that is overshadowed by individual differences. Panel A illustrates the stimuli used to assess different degrees of challenge to working memory. B and C show the increasing difficulty of the task as reflected in behavior. D shows the overall performance as measured with d'. Red points refer to females and blue to males.

However, in drawing this conclusion one must distinguish between sensation seeking, which does not appear to reflect imbalance, and impulsivity, which is a form of decision-making that is overly sensitive to immediate urges without adequate consideration of consequences. There are at least two forms of impulsivity that are relevant in regard to adolescent behavior (Winstanley et al., 2010). One called impulsive action reflects tendencies to act without thinking about consequences, also known as motor impulsivity (Patton et al., 1995; Romer et al., 2009). Acting without thinking is moderately positively related to sensation seeking, as well as the BAS and, also peaks during adolescence (Collado et al., 2014; Kasen et al., 2011; Shulman et al., 2015). A major difference between acting without thinking and sensation seeking is that, unlike sensation seeking, it is *inversely* related to WM ability (Khurana et al., 2012; Romer et al., 2011). This inverse relationship is understandable in that persons with this form of impulsivity lack the attentional control and capacity to consider alternatives to strong impulses.

Another form of impulsivity, known as impulsive choice (e.g., Mischel et al., 1989; Romer et al., 2010), reflects tendencies to choose smaller, immediate rewards over larger but delayed rewards (McClure et al., 2004; Metcalfe and Mischel, 1999). This preference for immediate reward is also inversely related to WM ability (Shamosh et al., 2008), again suggesting that weak ability to consider alternative courses of action predisposes to this form of impulsivity. Nevertheless, it is largely unrelated to sensation seeking (Cyders and Coskunpinar, 2011), which is not surprising given that it involves a choice between two rewards. Although it correlates with impulsive action, it does *not* exhibit a peak during adolescence. Rather it declines slowly from childhood onward, reflecting the increase in executive function during adolescence (Green et al., 1994; Romer et al., 2010; Steinberg et al., 2009; van den Bos et al., 2015). Thus, it is a simplification to assert that the adolescent period is marked by heightened impulsivity relative to children and adults considering that impulsive choice does not peak during this age period.

Although impulsive action and sensation seeking appear to conform to the stereotype of the impulsive adolescent, sensation seeking has different consequences from impulsive action. Research in both humans and other animals indicates that sensation seeking is positively correlated with PFC activation, while impulsivity displays the opposite tendency (Jupp and Dalley, 2014). Youth with high sensation seeking tendencies gravitate toward potentially risky activities, but in the absence of acting without thinking, they are less likely to experience adverse health consequences, such as addiction or problem gambling, than youth with impulsive tendencies (Khurana et al., 2017; Magid et al., 2007; Smith et al., 2007). These findings have remarkable parallels in the animal literature where it has been found that sensation-seeking lab rats are likely to try addictive drugs, but they are not likely to continue their use when it leads to adverse consequences (Belin et al., 2008; Winstanley et al., 2010). In contrast, rats that act impulsively are much more likely to develop addictive behavior that persists despite the maladaptive consequences. Lack of cognitive control, therefore, is more clearly characterized by impulsive action than sensation seeking.

Bjork and Pardini (2015) review the evidence regarding developmental changes in brain response to rewarding stimuli. Their review suggests that youth who exhibit harmful risk-taking tendencies exhibit brain responses consistent with weak cognitive control. However, this pattern is only representative of a subset of youth. Impulsive youth who lack self-control have been observed to display this characteristic at a young age and to continue to display poor control over behavior well into adulthood (Iacono et al., 2008; Moffitt et al., 2011; Reyna, 2012). Indeed, such youth are disproportionately likely to experience the hazards that arise during adolescence and beyond, as examples, higher rates of injuries and illnesses due to automotive crashes, violence, and sexually transmitted infections (Moffitt et al., 2011; Sourander et al., 2006). Nevertheless, it is important for both theoretical and pragmatic reasons to distinguish risk taking that arises due to interest in exploring the environment from a developmental deficit in cognitive control during the adolescent period.

We have observed the beginnings of the distinction between exploratory and impulsive risk taking in a longitudinal cohort one of us is studying in Philadelphia (Romer et al., 2009). Youth ages 13–15 who began to use drugs with increasing frequency were much more likely to be highly impulsive than sensation seeking. Sensation seekers at this age try drugs, but they do not typically exhibit progression in regular use (Khurana et al., 2015a). A similar pattern was observed for early sexual initiation (Khurana et al., 2012) and unprotected sex (Khurana et al., 2015b). Although high sensation seekers may explore novel behavior that can lead to harmful outcomes if continued, they appear to learn from these experiences as they age, while youth with impulse control problems do not. These patterns suggest that the increase in sensation seeking that characterizes adolescence does not necessarily lead to maladaptive behavior unless it is accompanied by weak executive function, such as exhibited by acting without thinking or the desire for immediate reward.

As suggested by Reyna and Farley (2006), there appear to be two divergent routes to heightened adolescent risk taking: one that is associated with a *greater* reliance on executive resources (energized by a greater drive toward sensation seeking) and one that is associated with *reduced* executive capability (impulsivity) (see also Chassin et al., 1989; Reyna et al., 2015b). Despite the dominant narrative that adolescents are impulsive, Reyna and Farley's (2006) overview of the literature suggests that much of adolescents' risk taking is characterized by a surprising "rationality" in the conventional economic sense (Institute of Medicine, 2011). That is, risk taking across many real-world domains is found to be a function of trade-offs between perceived risks and benefits—as contrasted with impulsive or emotional risk taking. If anything, many adolescents can be described as "hyper-rational," inasmuch as they rely on the risks and benefits of their behavior even more than adults do, which promotes risk taking when negative consequences are perceived to be unlikely (as is the case with many public health threats, such as contracting HIV).

Brain models that emphasize imbalanced development of limbic versus cognitive control regions suggest that adolescents are resistant to information about risks. Because the imbalance is "hard-wired," there is little one can do other than to shield adolescents from their otherwise natural risk tendencies (Steinberg, 2008, 2014). However, trends in the use of both legal and illegal drugs, as assessed since 1975 by the Monitoring the Future (MTF) study (Johnston et al., 2015a), indicate that adolescents are responsive to the harm that drugs can pose. These harms are transmitted through various channels, including media campaigns (Elder et al., 2004), school-based education (Faggiano et al., 2008), and parental and peer influences (Bahr et al., 2005). Indeed, use of popular substances such as tobacco, alcohol, and marijuana have declined since the survey began. Furthermore, the correlation in the MTF study between annual rates of use of these drugs and perceptions of risk associated with those drugs was $r = -0.83$ for alcohol, $r = -0.63$ for marijuana, and $r = -0.80$ for cigarettes. These patterns are suggestive of an adolescent brain that is sensitive to adverse consequences despite interest in exploring novel experiences. Contrary to stereotypes about adolescents, Reyna and Farley's (2006) overview of the literature showed that much adolescent risk taking was consistent with sensitivity to both perceived risks and benefits, which is a rational rather than impulsive process according to traditional views of rationality.

1.4. The importance of type of risk

Research concerning the imbalanced adolescent brain has taken a rather broad brush approach to the assessment of risk taking. In this section, we review what is known about developmental trends in risk taking as assessed in laboratory tasks and how different forms of risk taking are related to cognitive control. As previously noted, despite stereotypes of adolescents as more impulsive than either children or adults, there is considerable evidence that some risk-taking preferences (such as impulsive choice) do not peak during adolescence but instead follow a monotonic decline from childhood to adulthood. A developmental decline in risk taking is common in tasks in which the gains and losses attributable to different choices are explicitly defined or able to be learned quickly (Defoe et al., 2015). This kind of task, known as decision under risk, is different from ones in which the outcomes and associated probabilities are ambiguous or unknown, commonly known as decisions under ambiguity (Brand et al., 2006; Volz and Gigerenzer, 2012).

Assessments of impulsive choice fall under the rubric of decision under risk in that these paradigms explicitly provide information regarding the magnitude of reward and the likelihood of its occurrence as denominated by either delay or probability. Other tests of decision under risk provide choices between two or more alternative options that differ in reward and probability of outcome. A common task is one in which a certain positive option is contrasted with a riskier option even though the expected value of the risky option is equivalent to the certain option (e.g., win $2 for sure vs. equal chance to win nothing or $4) (see Levin and Hart, 2003). These tests also demonstrate a monotonic decline in risk taking in which children are *more* risk seeking than adolescents who are more risk seeking than adults. When different age groups are compared on other types of choice tasks in which a certain option is not available, the same decline is evident once IQ is held constant (Defoe et al., 2015). This control is important because it is difficult to arrange choice tasks that are understandable for children (e.g., under age 10; see also Reyna and Ellis, 1994).

Like Levin and Hart (2003) and Reyna and Ellis (1994), Paulsen et al. (2011, 2012) designed a task that was easily comprehended from childhood to young adulthood and found clear evidence for a decline in risk seeking whether a certain option was available or not. One explanation for this clear deviation from imbalance models as well as stereotypes of adolescent impulsivity is that adolescents are more risk seeking under ambiguity than children or adults (Paulsen et al., 2012). That is, given the potential for a reward but lack of information about its likelihood, adolescents will be more inclined to *explore* the risky option than either children or adults. As a result, they may actually exhibit a more rational response than adults who are notoriously risk averse when certain rewards are at risk.

In a demonstration of adolescent exploration, Tymula et al. (2012) showed that compared to adults, adolescents are more likely than adults to take risks that are ambiguous. As a result, their behavior was more "rational" in the economic sense of evaluating options based on expected value than adults. In their study, adults were so averse to unknown risks that they preferred expected values that were far smaller than adolescents were willing to tolerate. As they conjectured, "such a tolerance may make sense, because it would allow young organisms to take better advantage of learning opportunities." Adolescents' greater tolerance for ambiguity may also reflect their overly optimistic evaluation of the rewards of novel behavior (Romer, 2010; Romer and Hennessy, 2007). Exploration of novel environments has survival value and has been linked to activity in both PFC and subcortical regions (Daw et al., 2006), again suggesting that adolescents may not be structurally handicapped with respect to specific information-processing abilities that facilitate learning.

The evidence we have reviewed suggests that in characterizing adolescent risk taking, it is critical to distinguish between different types of risk behavior, each of which has unique motivational and cognitive underpinnings. We describe these different patterns in Fig. 5. Impulsive action is characterized by *insensitivity* to risk, a form of risk taking that peaks during early adolescence. However, it is only characteristic of a subgroup of youth with weak executive function and self-control, conditions that are present prior to adolescence (Bjork and Pardini, 2015; Kreuger et al., 2002; Moffitt et al., 2011). This form of risk taking is most clearly associated with the behavior that imbalance models seek to explain. In the absence of intervention, this form of imbalance can persist into adulthood. Impulsive choice as well as other forms of decision making under *known* risk do not peak during adolescence. Indeed, adolescents are more inclined to avoid risks than children under delay of reward or other forms of decision making under known risk. Finally, choice under *ambiguity* is sensitive to sensation seeking tendencies that encourage exploration, such as use of drugs (Romer and Hennessy, 2007). Although it may peak during adolescence, exploration and tolerance of ambiguity is not devoid of cognitive control and may actually be more adaptive in many circumstances than the extreme ambiguity avoidance exhibited by adults.

1.5. Do adolescent risk taking tendencies match predictions of imbalance?

If developmental imbalance between cognitive control and limbic activation were responsible for peaks in adolescent risk taking, one would expect those peaks to occur in mid-adolescence when imbalance is at its height (Willoughby et al., 2013). However, to the degree

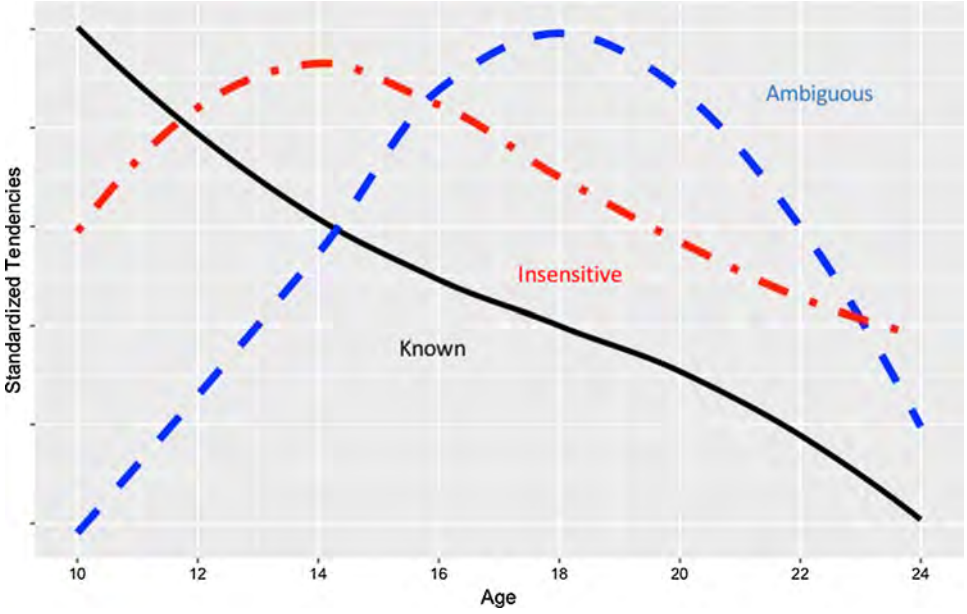

Fig. 5. Differences in three types of risk taking tendencies across age. Trends for Known and Ambiguous risks apply to all adolescents while the trend for Insensitive risk taking applies to youth with high levels of acting without thinking that precede adolescence and remain elevated into adulthood.

adolescents suffer injury, the period of highest risk occurs rather late in the transition to adulthood when inexperience is still high despite the nearly complete maturation of brain networks that are thought to enable cognitive control. For example, use of either cigarettes or marijuana peaks around age 20 in the U.S. (Romer, 2010); while binge drinking remains high throughout the third decade (Johnston et al., 2015b). Deaths due to overdoses of alcohol peak much later, around age 50 (Kanny et al., 2015), although younger drinkers may be more likely to overdose and survive. The proportion of driving fatalities attributable to alcohol peaks between ages 21 to 34 and continues at high rates until age 54 (US Census Bureau, 2012). Sexually transmitted infections such as gonorrhea and chlamydia peak between ages 20 to 24 (Centers for Disease Control and Prevention, 2014).

Conclusions about age trends in risk-taking must take risk opportunity and other co-occurring factors into account, as Shulman et al. (2016) note. In particular, research has shown that adult supervision of adolescents declines as they age, especially in males, thereby providing increasing opportunity to take risks (Gerard et al., 2008). However, with sensation seeking on the decline and cognitive control at its peak during early adulthood, any increases in unhealthy risk taking during this period would seem less attributable to imbalance than to stable individual differences in impulsivity that emerge prior to adolescence and remain evident into adulthood (Iacono et al., 2008; Moffitt et al., 2011). As adolescents enter young adulthood, they are presented with even greater risk-taking opportunities that will challenge those with weak cognitive control.

In summary, the appeal of the imbalance model rests in part on the popular stereotype of the adolescent as impulsive and lacking in cognitive control. Closer examination of this stereotype reveals that only one form of impulsivity (acting without thinking) peaks during adolescence and that this form of impulsivity varies significantly across individuals. The other major form of impulsivity, impulsive choice, declines from childhood to adulthood and thus is not likely to be explained by peaks in adolescent imbalance. In addition, other decisions under conditions of known risk also decline from childhood to adulthood. Finally, although sensation seeking does peak during adolescence, it is not characterized by the absence of cognitive control.

1.6. Evidence for structural imbalance

If imbalance does not characterize all types of risk taking behavior, what is the evidence regarding structural imbalance in brain development? Studies of brain structure and risk taking tend to produce confusing results, which is not surprising given that risk taking itself is a complex behavior. Some forms of risk taking can be positively related to executive function (e.g., decision under ambiguity) and others inversely related (e.g., impulsive action).

In normal development, gray matter loss in PFC is thought to be a marker of maturation, perhaps reflecting fine-tuning of brain structure (Spear, 2010). However, research examining structural brain development in relation to executive control has found that *less* prefrontal gray matter is associated with ADHD and forms of impulsivity that emerge early in development (Shaw et al., 2011; van Ewijk et al., 2012). Such persons also exhibit a lower rate of gray matter reduction as they age. With thinner cortical gray matter at the outset of adolescence, there may be less to prune. Thus, simple indices of gray matter reduction are unlikely to be a pure marker of enhanced cognitive control. Indeed, the development of brain structure varies with IQ in a complex interaction with age. Shaw et al. (2006) demonstrated that higher IQ is associated with *thinner* cortex in childhood, while in adolescents this relationship is reversed and *thicker* cortex is associated with higher IQ. A more recent longitudinal study of 504 participants corroborated this interaction with age, but suggested that the transition point may occur in early adulthood (age 21) rather than adolescence (Schnack et al., 2015).

Recent research suggests that patterns of gray matter change are location dependent and underlines the importance of white matter expansion occurring as a result of myelination. Vandekar et al. (2015) recently showed that gray matter reduction was maximal in sulci where white matter organization occurred. Multivariate analyses also revealed a second pattern, whereby gyral cortex thickened in early adolescence, a process that appears to asymptote by age 13. Thus, while this finding awaits replication in longitudinal studies, human neuroimaging research indicates that cortical *thinning* may be the result of both myelination and pruning, while cortical *thickening* characterizes a secondary maturation pattern that occurs during adolescence in more localized parts of gyral cortex. These more complex patterns of gray matter change further suggest that indices based on overall gray matter change are likely to obscure more complex organizational changes in brain structure as adolescents age. Indeed, it appears that the dominant pattern of brain development from childhood to adulthood is monotonic decline in gray matter associated with increases in myelination (Lebel et al., 2012). However, Berns et al. (2009) found that controlling for age, white matter maturation was *positively* related to a wide range of prior real-world risk behavior in adolescents, some of which may

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well be associated with exploratory drives. This pattern was recently replicated in an experimental context by Kwon et al. (2015). Nevertheless, other research finds that white matter integrity in some brain regions is weaker in children with ADHD, suggesting that some white matter deficits play a role in youth with this form of impulsivity (van Ewijk et al., 2012). In sum, there does not appear to be a simple relation between myelination and risky behavior. Developmental differences in myelination can be associated with *greater* rather than less risky behavior during adolescence, especially when the risks are ambiguous. On the other hand, conditions such as ADHD which are likely to reflect impulse control problems may be characterized by less white matter development.

Analyses of gray matter maturation in limbic regions also fail to conform to expectations of structural imbalance. Rather than reflecting early maturation in limbic structures, gray matter change continues well into adolescence (Dennison et al., 2013; Raznahan et al., 2014). A direct test of the structural imbalance model conducted by Mills et al. (2014) examined differential brain maturation in a longitudinal study of volume changes in the PFC versus the amygdala and the nucleus accumbens. Using three scans across childhood, adolescence, and young adulthood, these researchers found that the amygdala exhibited *increased* volume up to about age 16, when growth in this structure began to asymptote. The accumbens exhibited declining volume as adolescents aged. Using these limbic regions as indicators of imbalance in relation to maturation of the PFC, the researchers correlated individual differences in structural imbalance with reports of real-world risk taking. Consistent with the possibility that the risk taking recalled by those participants was a mixture of exploratory and impulsive behavior, there was no correlation between the imbalance observed in brain structure and reports of risk behavior during adolescence. Notwithstanding the study's sample size (n = 33), the authors "failed to find a relationship between the presence of a mismatch in brain maturation and risk-taking and sensation-seeking behaviors during adolescence." (p. 147).

The imbalance model advanced by Galván et al. (2006) suggested that ventromedial PFC (vmPFC) matures more slowly than the ventral striatum and that greater activation in the striatum relative to vmPFC could be the source of greater risk taking in adolescents. This model does not seem to follow from the original observation that brain maturation during adolescence proceeds from ventral to dorsal regions. Indeed, a recent study examining resting state connectivity between the striatum and ventral- and medial-PFC found that these regions exhibited early and rather stable connectivity from childhood to adulthood (Fareri et al., 2015).

It is important to note that Galván et al. (2006) based their conclusions on a reward learning paradigm in which adolescents have been shown to exhibit greater ventral striatal response to reward prediction errors than adults (see also Section 2.2 of this issue later in regard to Cohen et al., 2010). Thus, this heightened striatal response may not be a particularly sensitive indicator of maladaptive risk taking. Furthermore, as participants gained experience in the task, adolescents also showed an anticipatory vmPFC response suggesting that this region "predicted" the outcome of the reward cue, an ability that is associated with healthy vmPFC function (Rolls, 2014). Thus, if anything, this study showed greater functional synchrony between these regions in adolescents than in either children or adults, a finding potentially indicative of greater sensitivity to reward learning. A follow-up study by Galván et al. (2007) found that heightened ventral striatal activation in receipt of reward was a predictor of the likelihood of engaging in hypothetical real-world risk-taking; however, this was an individual difference, characteristic of both adults and adolescents.

Christakou et al. (2011) found that activation in vmPFC and connectivity with ventral striatum was related to age-dependent decline in impulsive choice. Consistent with the cognitive control predictions of imbalance models, but not the reward sensitivity predictions, this form of risk taking did not peak during adolescence. Thus, this study did not directly address the conditions underlying adolescent-specific imbalance.

In total, the findings suggest that white matter development and associated declines in gray matter are not clearly related to reduced risky behavior. Furthermore, connectivity between the striatum and vmPFC is established early in development such that adolescents need not be handicapped by inadequate linkage between these regions. Indeed, the evidence appears to be more consistent with the important role of the vmPFC in reward-based learning during adolescence, and the close connectivity between this region and the ventral striatum (Haber and Knutson, 2010; Rolls, 2014).

1.7. Other models of risky decision making

Other models of risky decision making also focus on the relative strength of cognitive control and reward sensitivity processes (Casey, 2015). However, these models do not require a structural deficit in the ability to exercise self-control. For example, McClure et al. (2004) find that within the same individuals, making less impulsive choices is associated with greater activity in PFC cognitive control regions, while during the same scanning session making impulsive choices is associated with ventral striatal activation. Nevertheless, in a recent developmentally sensitive study across ages 8–25, van den Bos et al. (2015) found that functional connectivity between medial striatum and cognitive control regions (dorsolateral and ventrolateral PFC) mediated declines in impulsive choice across age. However, as has been observed in other research (Green et al., 1994; Romer et al., 2010; Steinberg et al., 2009), discount rates declined rapidly from childhood to early adolescence and showed very little decline from that point onward. Thus, apart from individual differences, impatience may not be particularly relevant for understanding adolescent peaks in maladaptive adolescent risk taking. In addition, connectivity change was observed with the medial rather than ventral striatum, suggesting greater involvement with cognitive control than motivational functions of the striatum (Cools et al., 2008), a result consistent with the finding that sensation seeking and discounting are largely uncorrelated (Cyders and Coskunpinar, 2011; Romer et al., 2010).

The model of hot versus cold cognition proposed by Metcalfe and Mischel (1999) proposes that reducing the appeal of immediate (hot) rewards can be accomplished by flexible allocation of attention (e.g., thinking about something other than the reward). This model also focuses on the ability to delay gratification, a form of impulsive choice that does not peak during adolescence. Although the ability to allocate attention may increase with development, it is not a skill that is particularly impaired in adolescence relative to earlier ages, and variation in tendencies to delay gratification may well be driven by individual differences in life experience (McGuire and Kable, 2013).

The Driven Dual Systems model proposed by Luna and Wright (2015) also focuses on imbalance between cognitive control and dopamine driven reward motivation. Unlike the Casey model in Fig. 1, their model recognizes that cognitive control achieves adult levels by mid-adolescence. However, they suggest that the rise in dopamine activation during adolescence exceeds the levels experienced by adults, thereby predisposing toward immediate rewards in excess of adult levels. Nevertheless, Luna and Wright suggest that the sensation seeking that results from this imbalance has adaptive characteristics, such as the need to explore the environment. They also note that this imbalance "may make some adolescents vulnerable to risk-taking behavior' (p. 107). Luna and Wright use the term risk-taking to characterize maladaptive behavior by definition; but as we have noted, exploration is a form of risk-taking that need not be maladaptive. Thus, their model is consistent with our suggestion that the rise in maladaptive risk taking only characterizes some adolescents and thus accords with the analysis presented here.

Another model that has garnered significant attention in regard to adolescent brain development is the Triadic Model of Ernst and

colleagues (Ernst, 2014; Ernst and Fudge, 2009). This model is described by Ernst (2014) as a 'heuristic tool' for organizing neuroscience research on motivated behavior. The model not only considers imbalance between cognitive control and reward processing regions but also includes potential imbalance with avoidance processes centered in the amygdala and related regions. Ernst proposes that the three regions act to achieve an equilibrium that "varies across individuals."

The triadic model rightly expands the brain regions that must be considered in understanding developmental changes during adolescence. However, although the amygdala has input to the ventral striatum, it is sensitive to both rewarding and aversive events. Rather than serving to balance the ventral striatum, it may actually alert the ventral striatum to salient events that require action (Rolls, 2014). In their reviews of literature regarding reward processing, Richards et al. (2013) also note the wide differences that obtain depending on the laboratory task and the incentives provided to research participants. In some paradigms, adolescents exhibit control equal to adults, while in others they do not. However, even when adolescents appear to engage in less cognitive control than adults, this deficit can be overcome by increasing incentives for performance (Richards et al., 2013). In sum, the model may apply more to individual differences due either to experience or tendencies that exist prior to adolescence.

Casey (2015) also suggests that models of adolescent risk taking include interconnections between more than just the striatum and PFC. She highlights findings suggesting that compared to children and young adults, adolescents exhibit stronger emotional responses to laboratory stimuli. For example, adolescents commit more errors in a go/no-go task when the no-go cue is a smiling face compared to a neutral face. What is less clear is how these responses relate to real world risk taking. It may be that such responses are related to exploratory behavior, which is less likely to lead to harmful consequences than high levels of impulsive behavior. Other examples of emotional responses to emotional stimuli suggested that in some paradigms (but not others), adolescents react more strongly to aversive stimuli, such as fearful faces. But here again, it is not clear that these responses would lead to heightened or harmful risk taking, and in some cases, heightened adolescent response only characterized some adolescents, with others showing emotional responses comparable to children and adults (Hare et al., 2008). At this point, without the necessary clarifying information regarding the type of risk taking that is being examined, it is difficult to draw conclusions about such evidence.

In summary, our review of the evidence regarding structural differences in brain development suggest that the adolescent brain undergoes rapid change during this age period, but connections to maladaptive risk behavior depend on both individual differences and the type of risk taking. Evidence linking brain structure and function to risky behavior tends to be inconclusive regarding imbalance, and this is not surprising given the many ways that risk taking can manifest. Furthermore, cognitive control reaches maturity by early adulthood when sensation seeking is in decline but the adverse effects of risk taking begin to peak. Thus, the developmental imbalance that is suggested to be at the root of such adolescent risk taking is unlikely to explain this rather late appearance of developmental risk. We propose instead that for the majority of adolescents, maladaptive risk taking declines from childhood on. For those with heightened impulsivity, risks can continue to grow as opportunities for such behavior increase; however, this pattern is concentrated in a subset of youth who exhibit impulsive behavior prior to adolescence.

2. Cognitive control vs. experience-based cognitive development over the lifespan

Imbalance models suggest that cognitive control develops linearly during adolescence while sensation seeking peaks. Furthermore, Shulman et al. (2016) claim that cognitive control continues to grow well into young adulthood and that this helps to explain the continued rise in risk-taking during this period. Here we note that this presumed linear increase in cognitive control conflates two separate cognitive processes, one based on structural maturation of the cognitive control system and the other dependent on increasing connectivity between the PFC and parietal, occipital, and temporal cortices that build over time with experience (Fuster, 2009, 2013). When these are separated, it becomes clear that cognitive control also peaks by late adolescence and early adulthood while experience-based development continues in a monotonic fashion well into the aging process.

The distinction between cognitive control and experience-based cognitive development is consistent with recent research that has moved beyond simple models of gray matter change to more nuanced analyses of brain networks (Ernst et al., 2015; Pfeifer and Allen, 2012). An important study by Dosenbach et al. (2010) examined the development of functional brain networks from ages 7 to 30 using resting-state fMRI. Using a machine-learning approach, they showed that measures of functional connectivity could provide an index of brain network maturation that correlates with age. The most important features of this model are enhanced connectivity *within* large-scale functional brain networks, such as the executive control and default mode networks, but reduced connectivity *between* such networks during the adolescent age period (Baum et al., 2017; Stevens, 2016). Interestingly, analyses indicate an asymptote in functional network development by age 22, before presumed maturation of pruning and white matter growth has run its course. However, the dataset was somewhat sparse in the late adolescent age range, leaving open the possibility that the asymptote occurred even earlier (e.g., see Vaso et al., 2017). In addition, similar to the pattern of WM development observed by Satterthwaite et al. (2013a,b), the range of maturation of brain networks during the resting state varied widely across individuals. These patterns have been subsequently replicated in independent datasets controlling for confounds due to head movement (Fair et al., 2013; Satterthwaite et al., 2013b).

Rubia (2013) and Luna et al. (2010) summarize the changes in brain activation that occur in cortex from childhood to later adulthood. Their summaries indicate increasing connectivity within cognitive control networks as children age, which may contribute to greater cognitive control during adolescence. This conclusion is consistent with recent studies indicating that brain networks involved in cognitive control versus default mode become more segregated during adolescence (Baum et al., 2017; Dosenbach et al., 2010; Fair et al., 2008; Satterthwaite et al., 2013), but conversely become less segregated during later adulthood, *thereby displaying an inverted-U shaped pattern of interconnectivity across the lifespan* (Betzel et al., 2014; Chan et al., 2014). Furthermore, Chan et al. (2014) found that reduced network segregation at any adult age was associated with an important marker of age-related cognitive decline, namely weaker verbatim memory. As summarized by Betzel et al. (2014), on the one hand, functional connectivity (FC) over the lifespan *within* resting state networks (RSNs) "decreased with age, affecting higher-order control and attention networks. On the other hand, FC tended to increase *between* RSNs, especially among components of the dorsal attentional network, the saliency/ventral attention networks and visual and attention networks and the somatomotor network." (p. 352).

These changes are consistent with a brain that grows in cognitive ability during adolescence but that increasingly relies on between-network connections as adulthood progresses into aging. For most adults, the ability to exert cognitive control or behavioral inhibition eventually declines as indexed by tasks that challenge response speed and attentional skills (e.g., stop-signal and WM) (Lindenberger, 2014). However, older adults have greater ability to draw from experience, which is consistent with growing connectivity between networks.

2.1. The importance of experience

Despite the stereotype of adolescents as impulsive risk takers, it is

important to consider the role of exploration and learning that occurs during this period of development. Fuster (2009, 2013) proposes a model of brain development across the neocortex involving what he calls *cognits* or networks of neuronal connections between the PFC and other cortical regions that build over time. Cognits provide a bridge between "executive memory" in the PFC and sensory and "perceptual memory" in other regions. These memories enable a form of what Goldberg (2006) calls "executive intelligence" built from experience in encountering novel problems. These networks are assumed to develop in a hierarchical manner, such that individual experiences reside at the lowest level of the network. As experience accumulates, more abstract levels of memory are formed that enable clearer decision rules for action across similar domains. These more abstract memories provide experienced actors with shortcuts to decision-making that require less cognitive effort than less experienced adolescents might have to exert.

Fuster's theory of cognits is also broadly consistent with fuzzy-trace theory advanced by Reyna and colleagues, who highlight the importance in decision-making of a distributed system of gist in the brain, as opposed to localized verbatim, memory representations (Reyna et al., 2015b; see Reyna and Huettel, 2014, for differences in neural substrates). Fuzzy-trace theory emphasizes the accumulation of experience that leads to more adult-like decision-making and *gist-based intuition* (Reyna and Brainerd, 2011; Wilhelms et al., 2015). As people gain experience in a decision domain, they begin to *understand* patterns in the outcomes that accrue, a process that enables them to rely on more abstract gist principles regarding those decisions and less on the literal rewards and costs of a particular decision. This experience encoded in durable gist memories would be expected to facilitate decision-making (Fuster, 2009; Goldberg, 2006; Reyna and Lloyd, 2006; Reyna and Mills, 2014). Although late adolescents and young adults have greater cognitive control than the average older adult, they may not have developed the insight from experience, or what is conventionally called wisdom, that is important for functioning in the world (Reyna et al., 2011). Such experience would convert many ambiguous risk situations to ones with known risks that elicit less risk taking with age.

Research on cognition has shown that people mentally represent information about decision options in two ways: verbatim representations of details, which are precise enough to support analytical thinking, and gist representations, which are less detailed (i.e., fuzzy) and support impressionistic, parallel, and typically unconscious thinking (similar to characterizations of intuition; Reyna, 2012). The preference to rely on gist grows with experience, and, for risk and probability, the simplest gist is categorical, for example, the categorical distinction between some risk or no risk (e.g., Reyna et al., 2014; Reyna and Ellis, 1994). As adolescents age, it would be expected that they would also increasingly rely on gist-based reasoning when confronted with potentially maladaptive risk taking. The growth of reliance on more abstract gist memories from childhood to adulthood, as predicted by fuzzy-trace theory, has been replicated in 53 out of 55 studies on gist-based "false" memories (Reyna, 2011).

Consistent with a monotonic decline in risk taking with unambiguous risks, there is evidence that adolescents with better executive function perform better on such tasks (Brand et al., 2006; Khurana et al., 2015a; Shamosh et al., 2008). This evidence suggests that the decline that occurs with development can be attributed in part to increasing ability to store and compare outcomes of risky decisions. Such ability would also lead to better integration of experience when confronting risky situations, including reliance on gist-based memories. As a result, preference for maladaptive risk taking in specific domains would be expected to decline as experience accumulates and to do so more rapidly for youth with better executive function.

The meta-analysis by Defoe et al. (2014) (see also Tymula et al., 2012) contrasted the predictions of fuzzy-trace theory versus imbalance theories in laboratory tests of risk taking. The finding that risk taking declines with age, especially when a certain option is available, is not anticipated by imbalance theories. The presence of a certain versus risky option provides a critical test of contrasting theoretical predictions (e.g., see Kühberger and Tanner, 2010). Fuzzy-trace theory predicts that a gist representation favors the selection of the certain option for gains, a preference that grows with experience. Experiments on the development of risk taking confirmed that, in addition to motivational and cognitive control factors, risk preference is a function of competing verbatim versus gist mental representations of decision options. From the perspective of gist-based intuition, risking HIV infection by having unprotected sex is a bad idea even if the risks are low and the benefits are high (see Reyna, 2008). These theoretical ideas explain the otherwise puzzling (but predicted and replicated) result that experience, both from childhood to adulthood and from novice to expert in a specific domain of decision making, is associated with greater reliance on gist-based intuition rather than verbatim reasoning (e.g., Reyna et al., 2011; Reyna and Lloyd, 2006).

The greater verbatim information-processing efficiency of adolescents (relative to children and aging adults) would appear to be a benefit that compensates for their lack of experience. Adults progressively lose the ability to exert cognitive control over their attention and WM capacities (Lindenberger, 2014), leading to what Goldberg (2006) has termed "The Wisdom Paradox." With aging, the neocortex continues to lose gray matter in PFC with associated reductions in the ability to remember verbatim details of past experience and to hold information in WM (Chan et al., 2014; Dennis et al., 2013). Adults experience a domain-general decline in verbatim cognitive skills starting in the third decade of life (Tucker-Drob, 2011; Lachman et al., 2014), although gist memory is conserved (e.g., Brainerd et al., 2009; Reyna, 2012). During the same period of verbatim decline, the brain is estimated to lose about 7% of its striatal dopamine transporters per decade (Volkow et al., 1996), with even larger declines in the PFC (Eppinger et al., 2011). These declines, which begin in the third decade of life, are associated with reductions in various cognitive and motor functions, including episodic and working memory, inhibitory control, and switching (Bäckman et al., 2010; Li et al., 2010; Volkow et al., 1998). Yet, consistent with conservation of gist-based intuition, older adults' risky decision-making remains largely indistinguishable from that of younger adults when verbatim memory is not required (Mata et al., 2011; Samanez-Larkin and Knutson, 2014). Although adults are able to make good, and perhaps even better decisions than adolescents, they rely on their accumulated experience to counterbalance the declines in executive function that they once possessed in late adolescence and early adulthood.

From the perspective presented here, experience making risky decisions during adolescence, as executive functions develop, fosters increased development of gist-based reasoning. This experience is especially critical because it allows adults to avoid unhealthy risks using cognitive capacities (i.e., gist memory) that are preserved over a lifetime and that are robust in stressful or emotional situations (e.g., Reyna and Brainerd, 2011; see Reyna, 2011, for estimates of verbatim and gist memory, as well as cognitive control, across the lifespan). The growth in this ability reflects increasing wisdom, defined as the accumulation of gist-based insight and expert knowledge about the conduct and management of life challenges (Baltes and Smith, 2008; Baltes and Staudinger, 2000; Sternberg, 2001).

From a neurodevelopmental perspective, wisdom most likely involves the maturation (including pruning) and interconnection of several brain regions that enable the individual to harness experience in an adaptive fashion (Meeks and Jeste, 2009; Reyna and Huettel, 2014). These include the executive control and limbic systems. The default mode network including medial PFC plays an important role by facilitating self-referential processing, empathy, theory of mind, and future projection (Buckner et al., 2008; Meeks and Jeste, 2009). As noted, this system exhibits increasing intra-connectivity during adolescence (Fair et al., 2008; Sherman et al., 2014; Supekar et al., 2010). Nevertheless, it is the integrated functionality between systems across development that distinguishes wisdom from a simple top-down impulse control system

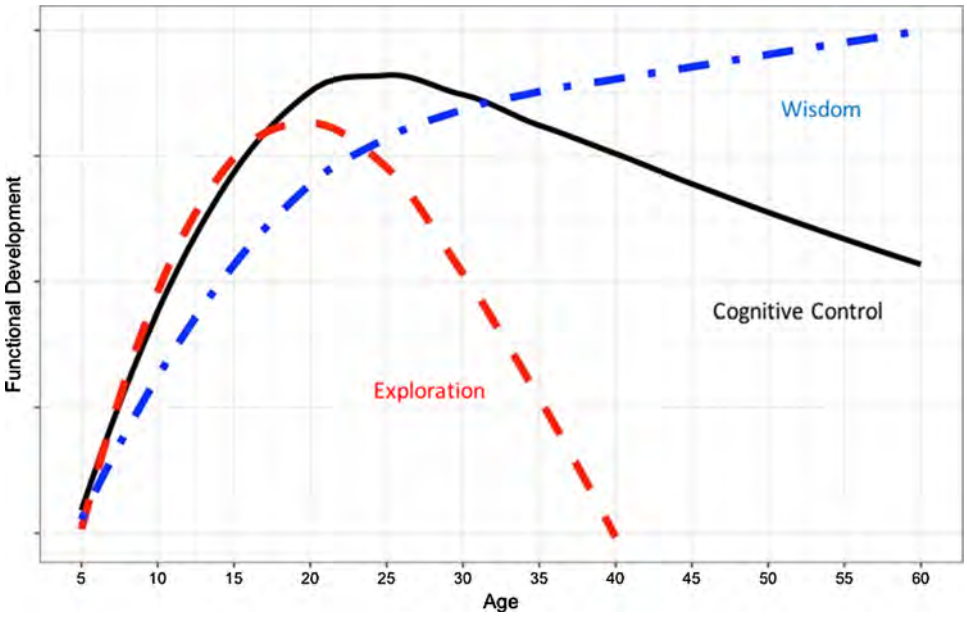

Fig. 6. Hypothesized trajectories of the Life Span Wisdom Model of cognitive control, exploration, and experience. Y axis scale is arbitrary.

(Reyna et al., 2015b).

We summarize the changes that occur relevant to adaptive decision making over the lifespan in Fig. 6. This model differs from imbalance models in several respects but most importantly by including a third trajectory representing the accumulation of experience and hence wisdom. Executive function displays an inverted U-shape function that peaks in late adolescence and early adulthood (Lachman et al., 2014; Lindenberger, 2014; Williams et al., 1999). At the same time as executive function is improving during adolescence, the rise in sensation seeking and related dopamine expression drives exploration of the environment which peaks earlier than executive function but subsides during later years (Mata et al., 2016). However, as we describe below, as a result of these two processes, the brain builds networks of experience that foster greater ability to make adaptive decisions in later adulthood despite the decline in executive function (Richards and Hatch, 2011; Webster et al., 2013). Thus, the rise in exploration that characterizes the adolescent brain serves an adaptive purpose of building robust representations of experience.

The model also recognizes that the late adolescent and young adult brain is still a work in progress during the period when exploration and wisdom are growing despite having reached the peak in cognitive control. Thus, late adolescents and young adults will still be exploring their world during this period and taking risks many of which can be adaptive. For those with especially weak cognitive control however, this period may produce particularly unhealthy consequences, such as addiction and unintentional injuries, many of which were foreshadowed by earlier impulsive behavior.

2.2. The adaptive adolescent brain

Although heightened sensation seeking makes novel and potentially risky behavior more common during adolescence, this risk taking may be motivated by a "rational calculus" (Reyna and Farley, 2006) that may be adaptive for learning that underlies brain maturation (see also Ellis et al., 2012; Luciana, 2016; Telzer, 2015). A study by Cohen et al. (2010) illustrates the adaptive character of the adolescent brain. In this study, adolescent participants (ages 14–19) showed a stronger dopaminergic brain response to reward prediction errors when engaging in a learning task than either younger children (ages 8–12) or adults (ages 25–30) (see also Galván et al., 2006, discussed above). Prediction error is considered important in motivating learning (Pagnoni et al., 2002; Schultz et al., 1997) and suggests that adolescents can take advantage of such error feedback as they explore the environment. Although the authors interpreted the finding as consistent with the hypothesis that adolescents engage in riskier behavior than younger or older persons, the task did not involve risky decision-making and thus was also consistent with the conclusion that adolescents are disproportionately primed to take advantage of positive feedback in a learning situation (see also Davidow et al., 2016; Satterthwaite et al., 2012).

Murty et al. (2016) recently proposed a model of experience-based brain development termed the Experience-Driven Adaptive Cognitive Model of adolescence that highlights the role of dopamine activation during adolescence as a modulator of enhanced memory-circuit integration between the hippocampus (HPC) and PFC. They review evidence indicating the importance of this process for building long-term memory representations that enable the use of experience to further more adaptive decision making. In particular, abundant evidence from studies in animals suggests that dopamine release from neurons in the midbrain plays an important role in the coding of reward prediction errors and uncertainty (Fiorillo et al., 2003; Tobler et al., 2005). In humans, such signals play an important role in episodic memory formation (Shohamy and Adcock, 2010), and tonic levels of midbrain dopamine activation may encourage exploration and acquisition of long-term memories that support learning and adaptation (Düzel et al., 2010). As Murty et al. (2016) say, "…different lines of research provide compelling support for adolescence being a unique period of plasticity and refinement of HPC-PFC circuits for the establishment of contextually-relevant responses to guide and optimize goal-oriented behaviors." (p. 54). Their model is consistent with the suggestion that the exploratory behavior motivated by dopaminergic activation during adolescence serves adaptive purposes.

A study of adolescent decision-making in the presence of reward reversal also supports the adaptive character of the adolescent brain. When confronted with changing reward contingencies, adolescents exhibited heightened activation of insular cortex, which was associated with more rapid reversal learning (Hauser et al., 2015). Young adults were slower to respond to the changes in contingencies. Recognizing such changes in contingencies is evidence of engaged executive function. These results suggest a possible mitigating factor (that adolescent brains are quick to recognize changes in reward contingencies), offsetting to some degree their heightened sensation seeking or attraction to novel experience.

Interestingly, youth with higher sensation seeking exhibit less impulsive choice as they age. In a national sample of adolescents and

young adults, Romer et al. (2010) found that high sensation seekers, who were more likely to engage in risky behavior than low sensation seekers, also exhibited higher levels of the ability to delay gratification as they aged, an important indicator of reduced impulsivity and cognitive control (Casey et al., 2011). Indeed, they reached higher levels of patience than youth who were lower in sensation seeking. Thus, experience gained during risk taking can lead to more adaptive decision-making over the long term, especially among those with sufficient cognitive skills, such as WM, to integrate their experience for future behavior.

Risk taking during adolescence has been described as normative. For example, Baumrind (1987) argued that "risk taking behavior characterizes normal adolescent development." (p. 98) Furthermore, "…some experimentation – be it with drugs or sex or odd diets or new ideas – is typical, and may even be an essential component, of a healthful adolescent experience and contribute to optimal competence." (p. 98) Some studies have shown that adolescents who experimented with drugs were more socially accepted by peers (Lightfoot, 1997; Maggs et al., 1995) and exhibited better adjustment than those who completely abstained from drug use (Shedler and Block, 1990). Chassin et al. (1989) observed that youth higher in sensation seeking engaged in what they called "constructive" risk taking, characterized by desire for independence and academic success, whereas "destructive" risk takers were characterized by impulsivity and antisocial tendencies. In a longitudinal study across grades 5–10, Lewis-Bizan et al. (2010) observed that youth who were characterized as possessing positive developmental attributes, such as competent control over behavior, were also likely to engage in risky behavior. However, their risk taking did not continue at high levels later in adolescence.

In some statements of imbalance models (e.g., Casey and Caudle, 2013; Spear, 2013), the importance of individual differences in adolescent risk taking is acknowledged. Nevertheless, the lower ability of the adolescent to control socioemotional decisions continues to be cited as a common deficit in adolescent brain function. For example, studies using driving simulation tasks by Steinberg and colleagues (e.g., Chein et al., 2011) are interpreted to show that adolescents' brains respond impulsively to the presence of their peers (Steinberg, 2014), whereas adults are less susceptible to these influences. Although peer effects may be stronger in adolescents, the direction of such effects appears to depend on the characteristics of those peers. Simply placing adolescents behind the wheel with peers in the vehicle does not necessarily produce riskier driving (see Romer et al., 2014, for a review). In particular, greater risk taking in the presence of peers is consistent with a group polarization effect of peer influence, such that when drivers think peer passengers expect them to drive aggressively, they are more likely to do so. However, when peers are not expected to hold these preferences, adolescent drivers are no more likely to drive in a risky manner (Bingham et al., 2016; Simons-Morton et al., 2014).

It is likely therefore that youth with relatively good executive control and peer groups with similar characteristics will be able to experiment with risky behavior without advancing to more serious outcomes (Lightfoot, 1997). However, as our analysis suggests, some youth will experience premature pregnancy, substance use, and other maladaptive behaviors that adversely affect educational attainment, health, and other social outcomes (Institute of Medicine, 2011).

3. Beyond imbalance during adolescence

Despite the valuable insights spurred by imbalance models, it time to move beyond these models to consider the role that experience plays in healthy adolescent development. One potentially fruitful direction in future research would be to compare measures of gist learning and decision making to measures that capture the development of wisdom (Sunstein, 2008; see also, Reyna, 2008; Reyna and Huettel, 2014). Such a direct comparison would test Reyna and Brainerd's (2011) fuzzy-trace theory, which predicts that decision-making shifts from relying on lower-level (verbatim) representations that encourage risk taking to more abstract (gist) representations that support healthier decisions to categorically avoid catastrophic risks (but to take risks when they offer the possibility of a categorically superior outcome relative to less risky options). In this regard, the theory has already successfully predicted self-reported real-world risky behaviors using gist measures (e.g., Broniatowski et al., 2015; Fraenkel et al., 2012; Mills et al., 2008; Reyna et al., 2011; Reyna and Mills, 2014; Wolfe et al., 2015).

Another promising direction for future research is to examine the relation between executive functions such as WM and the decline in maladaptive risk taking with age. As the consequences of exploratory risk taking accumulate in experience, those with stronger WM should be able to incorporate those experiences more effectively in decisions entailing maladaptive risk. Preliminary evidence for this prediction has been observed in a study of late adolescent risk for drug addiction. Those with stronger WM ability were more able to avoid advancing to drug dependence apart from differences in impulsive tendencies (Khurana et al., 2017).

Our model also suggests that we look at risk taking more broadly than just examining behaviors with adverse consequences. For example, Romer et al. (2016) showed that both sensation seeking and parts of the BAS were related to risk behaviors that are considered adaptive, such as entering scholastic competitions and engaging in sports (see also Hansen and Breivik, 2001). Many of the risky behaviors that adolescents pursue involve potential social conflicts with parents or peers (Weber et al., 2002), and these and other forms of risk behavior are also likely to increase during adolescence and should be considered in our models.

We have said little about sex differences, but as is evident in Fig. 2, there are gender differences in sensation seeking (Cross et al., 2011), which will have implications for different types of risk taking during adolescence. The correlation between sensation seeking and impulsive action is consistent with a smaller but established sex difference in measures of impulsive action (Cross et al., 2011), corresponding to the risk insensitive trajectory in our model in Fig. 5. This trajectory helps to explain the well-established over-representation of males in externalizing behavior, a pattern that begins early in development among youth with weak cognitive control (Bjork and Pardini, 2015; McGue and Iacono, 2005; Moffitt et al., 2011). On the other hand, the small relation between sensation seeking and decisions under known risk is consistent with the lack of sex differences in decisions under known risk (Cross et al., 2011). Nevertheless, the differences in sensation seeking would suggest that females are less inclined to engage in exploratory risk taking. However, many of the rewarding aspects of such behaviors are likely to be domain specific, such that young women may engage in exploration if they perceive the rewards to be sufficiently strong (Romer and Hennessy, 2007; Santos et al., 2016), for example in social domains (Weber et al., 2002). Future research should examine this possibility as well.

Finally, much remains to be learned about the organization of RSNs during the transition to adulthood. It is already known that youth with ADHD have weaker ability to suppress the default mode network (DMN) than normally developing youth (Kessler et al., 2016; Posner et al., 2014). This is evident in stronger connectivity between the DMN and task-positive networks in youth with ADHD. Youth with externalizing disorder and elevated levels of impulsive action exhibit the same pattern (Inuggi et al., 2014; Kessler et al., 2014; Shannon et al., 2011). Future research could identify the neural basis of this deficit and explore potential interventions that could reduce it (Kelly and Castellanos, 2014; Stevens, 2016). These leads could be followed to determine the neural basis of harmful forms of impulsivity as opposed to exploratory forms of risk taking that emerge during adolescence. Research regarding the functional roles of RSNs as they respond to growth in experience and wisdom during the adolescent period would appear to be a fruitful avenue of future research.

As more is learned about the growth of wisdom over the lifespan, it

Table 1
Differences between Imbalance Models and Lifespan Wisdom Model.

Imbalance Model	Life-span Wisdom Model
Slower development of PFC and its connection with limbic system results in imbalance that outweighs cognitive control over impulsive urges during adolescence (Fig. 1).	Cognitive control and dopaminergic activation rise in tandem during adolescence; much of adolescent risk taking is exploratory in keeping with the role of dopamine as a signal for novel reward (Fig. 6).
Rise in risk taking and incidence of health compromising behavior during adolescence reflects developmental imbalance.	Risk taking takes at least three forms, with different developmental trajectories (Fig. 5). The form most closely associated with imbalance reflects insensitivity to risk and applies primarily to youth with early elevated levels of impulsive behavior.
Peak in sensation seeking during adolescence produces more risk taking than in children or adults.	Peak in sensation seeking during adolescence motivates greater exploration in ambiguous environments, but risk taking declines monotonically from childhood to adulthood when risks are known, per greater reliance on gist and increasing executive function (Fig. 5).
Imbalance leads to increased injury and maladaptive outcomes during adolescence.	Timing of many maladaptive outcomes occurs in early adulthood when imbalance should be minimal; maladaptive outcomes are more related to high levels of impulsivity combined with risk opportunity and inexperience than to developmental imbalance.
Socioemotional influences excite the dopaminergic system and promote risk taking.	Socioemotional influences can promote risk taking, but social experience (interacting with peers) and positive social influences can promote healthy risk avoidance.
Main emphasis on brain maturation, rather than experience or interventions that can promote adaptive brain development. No predictions about life-span cognitive control or increase in wisdom.	Acknowledges brain maturation that reflects growth in experience and potential interventions to promote healthy decision making by increasing reliance on experience and wisdom.

is also important not to overplay the wisdom of adulthood. Just as stereotypes regarding adolescence have colored our interpretation of brain research, it is just as easy to romanticize the experience and wisdom of adulthood. Research shows that relying on gist can lead to predictable biases even in experts (see Wilhelms et al., 2015). The increasing aversion to risk in ambiguous contexts may also lead to less than optimal search tendencies (Tymula et al., 2012). A good deal of research in decision making over the past several decades reveals how heuristics and biases common in adults can produce fallacies in judgment (Kahneman, 2013; Stanovich, 2011). This classic research serves as the foundation of more recent approaches, such as fuzzy-trace theory, that account for fallacies in adulthood but also explain the strengths of mature decision making (Defoe et al., 2014; Reyna et al., 2014).

In conclusion, we have presented an alternative model of adolescent brain development that emphasizes the accumulation of experience as adolescents age and transition to adulthood, with concomitant changes in judgment and decision making (see Table 1 for a summary of differences between the Life-span Wisdom Model and Imbalance Models). The model explains much of the apparent increase in adolescent risk taking as an adaptive need to gain the experience required to assume adult roles and behaviors. The risk-taking that reflects lack of control or excessive sensitivity to immediate rewards is primarily an individual difference that characterizes some persons from an early age that can persist well into adulthood. At the same time, the adolescent brain is supremely sensitive to the learning that can occur during this period and has cognitive capacities to take advantage of the experience gained. The result is a brain with integrated circuits encompassing executive function (i.e., cognitive control and inhibition), as well as verbatim and gist memory networks, which can be called upon to negotiate both novel and familiar situations. The preservation of robust gist thinking maintains wise decision making during later adulthood when cognitive control capacities diminish. We believe this approach is more aligned with the scientific evidence, including results that challenge stereotypes about the adolescent brain.

Conflict of Interest

None.

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Erratum

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Coercive neuroimaging, criminal law, and privacy: a European perspective

Sjors L.T.J. Ligthart

Tilburg University, Department of Criminal law, PO Box 90153, 5000 LE Tilburg, The Netherlands
E-mail: s.l.t.j.ligthart@uvt.nl
PhD candidate, supervised by Prof. Dr. Tijs Kooijmans and Prof. Dr. Gerben Meynen. The findings that are presented in this chapter are derived from the author's current PhD project.

ABSTRACT

Different studies have shown that neuroimaging technologies can contribute to answering crucial legal questions of criminal law, generally regarding guilt, legal insanity and the risk of recidivism. However, the use of neuroimaging in criminal law also raises important legal questions. One of those questions is whether neuroimaging should be applied *coercively* to defendants and prisoners in light of privacy considerations. This paper examines this question regarding the European legal context. I argue that most neuroimaging applications yield data, which is, in terms of privacy sensitivity, no more sensitive than data acquired through current methods of criminal investigation, such as compulsory DNA testing. Therefore, I argue that some types of coercive neuroimaging will, in general and under certain specific conditions and safeguards, not contravene the right to privacy as set out in Article 8 of the European Convention on Human Rights. I suggest that while on the one hand one could advocate the need for a novel, specific European human right to mental privacy, on the other hand, it is possible to argue that such a right may be superfluous in respect of the use of existing neuroimaging technologies.

KEYWORDS: Neurolaw, Privacy, Forensic neuroimaging

INTRODUCTION

In 2015, four studies were published in this journal, which examined the way in which neurobiological information is being used in the criminal justice systems of the USA, Canada, England and Wales, and the Netherlands.[1] Recently, similar studies have also

1 Nita A. Farahany, *Neuroscience and Behavioral Genetics in US Criminal Law: An Empirical Analysis*, 2 J. Law Biosci. 485 (2015); Jennifer A. Chandler, *The Use of Neuroscientific Evidence in Canadian Criminal Proceedings*,

been published covering both the Slovenian and Australian legal approaches.[2] These studies show that neuroimaging technologies can contribute to addressing crucial criminal law issues, such as guilt, legal insanity, fitness to stand trial, and the risk of recidivism. However, the use of neuroimaging for criminal law purposes also *raises* important legal issues.[3] One of these is whether neuroimaging technologies should be applied *coercively* to defendants and prisoners in light of privacy considerations. In the USA, this question has been considered quite extensively: for example by Nita Farahany, Francis Shen, Michael Pardo, and Dennis Patterson.[4]

Although a similar question arises in the European legal context,[5] this question has received little attention.[6] Therefore, this paper poses the following question: how does coercive neuroimaging in criminal law relate to the right to respect for private life as laid down in Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR)? In my view, most neuroimaging applications yield data, which is, in terms of privacy sensitivity, no more sensitive than data acquired through current methods of criminal investigation, such as compulsory DNA testing. Therefore, I argue that some types of coercive neuroimaging will, in general and under certain specific conditions and safeguards, not contravene the right to privacy as set out in Article 8 of the ECHR. Furthermore, I suggest that while on the one hand one could advocate the need for a novel, specific European human right to mental privacy,[7] on the other hand, it is possible to argue that such a right may be superfluous in respect of the use of existing neuroimaging technologies. Although the neuroscientific, philosophical, and ethical underpinnings of neuroimaging applications are an important topic in the neurolaw debate,[8] this paper only focusses on the *legal* implications of coercive use of such applications in light of the right to privacy.

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2 J. Law Biosci. 550 (2015); Paul Catley & Lisa Claydon, *The Use of Neuroscientific Evidence in the Courtroom by Those Accused of Criminal Offenses in England and Wales*, 2 J. Law Biosci. 510 (2015); C. H. de Kogel & E. J. M. C. Westgeest, *Neuroscientific and Behavioral Genetic Information in Criminal Cases in the Netherlands,* 2 J. Law Biosci. 580 (2015).

2 Miha Hafner, *Judging Homicide Defendants by Their Brains: An Empirical Study on the Use of Neuroscience in Homicide Trials in Slovenia,* J. Law Biosci. (2019), DOI:\ignorespaces10.1093/jlb/lsz006; Armin Alimardani & Jason Chin, *Neurolaw in Australia: The Use of Neuroscience in Australian Criminal Proceedings,* Neuroethics (2019), DOI:\ignorespaces10.1007/s12152-018-09395-z.

3 Henry T. Greely, *Mind Reading, Neuroscience, and the Law*, in A Primer on Criminal Law and Neuroscience (S. J. Morse & A. L. Roskies eds., 2012); Sjors Ligthart, Thomas Douglas, Christoph Bublitz & Gerben Meynen, *The Future of Neuroethics and the Relevance of the Law*, 10 AJOB Neurosci. 120 (2019).

4 Nita A. Farahany, *Searching Secrets*, 16 U. Pa. L. Rev. 1239 (2012); Francis X. Shen, *Neuroscience, Mental Privacy, and the Law*, 36 H. L. Rev. 653 (2013); Michael S. Pardo & Dennis Patterson, Minds, Brains, and the Law: The Conceptual Foundations of Law and Neuroscience (2015).

5 R. Encinas de Muñagorri & C. Saas, *France. Is the Evidence Too Cerebral to Be Cartesian?*, 104 in Legal Insanity and the Brain: Science, Law and European Courts (Sofia Moratti & Dennis Patterson eds., 2016); Paul Catley, *The Future of Neurolaw*, 22 Eur. J. Curr. Leg. Iss., 1 (2016); Elena Rusconi & Timothy Mitchener-Nissen, *Prospects of Functional Magnetic Resonance Imaging as Lie Detector*, 7 Front. Hum. Neurosci. 1, 8 (2013).

6 D. van Toor, Het Schuldige Geheugen? Een Onderzoek Naar Het Gebruik Van Hersenonderzoek Als Opsporingsmethode in Het Licht Van de Eisen Van Instrumentaliteit en Rechtsbescherming (2017).

7 See on this topic Marcello Ienca & Roberto Andorno, *Towards New Human Rights in the Age of Neuroscience and Neurotechnology,* 13 LSSP (2017); Jan Cristoph Bublitz, *My Mind is Mine!? Cognitive Liberty as a Legal Concept*, in Cognitive Enhancement (E. Hildt & A. Francke eds, 2013).

8 For this, see *i.a.* Pardo & Patterson, *Supra* note 4.

The outline of this paper is as follows. Section 2 briefly mentions four neuroimaging applications and the way in which they could contribute to answering crucial questions of criminal law. Section 2 also describes two types of coercion, which can be used in order to apply different neuroimaging applications. Section 3 describes the general meaning and scope of the right to privacy contained within Article 8 ECHR. Thereafter, Section 4 compares coercive neuroimaging in criminal law to current methods of criminal investigation, within the context of the right to privacy. Subsequently, Section 5 examines the legal implications of the right to privacy for coercive neuroimaging in criminal law (which I also call 'coercive forensic neuroimaging'). The results of this analysis are discussed in Section 6.

COERCIVE FORENSIC NEUROIMAGING

Neuroimaging technologies enable us to examine our brains and their activity. In general, two types can be distinguished: structural and functional neuroimaging.[9] While structural neuroimaging technologies, like MRI and CT, show the biological structures of someone's brain (brain anatomy), functional neuroimaging, like fMRI and EEG, measures brain activity (indirectly), which can yield information about how someone's brain functions. Much research has been done regarding possible forensic applications of these neuroimaging technologies. Here, I focus on four categories of neuroimaging applications that can yield specific brain-related information and could therefore contribute to answering central questions of criminal law:[10]

I. Brain-based lie detection,[11]
II. Brain-based memory detection,[12]
III. Diagnostic neuroimaging, and[13]
IV. Neuroimaging to predict future dangerousness ('neuroprediction').[14]

Through acquiring information from the brain of 'the subject', these four neuroimaging applications, each in their own way, may be very helpful to answering crucial questions of criminal law. Neuroimaging may assist in determining guilt, legal responsibility, fitness to stand trial, and the risk of recidivism.[15] As well as these four methods, more

9 Sarah Richmond, *Introduction,* in 3 I Know What You're Thinking: Brain Imaging and Mental Privacy (Sarah Richmond, Geraint Rees & Sarah J. L. Edwards eds., 2012).

10 For a brief discussion of these categories, see Sjors L. T. J. Ligthart, *Coercive Neuroimaging Technologies in Criminal Law in Europe. Exploring the Legal Implications for the Prohibition of Ill-Treatment (Article 3 ECHR)*, 87–89 in Regulating New Technologies in Uncertain Times (Leonie S. Reins ed., 2019).

11 Martha J. Farah et al., *Functional MRI-Based Lie Detection: Scientific and Societal Challenges*, 15 Nat. Rev. Neurosci. 123 (2014).

12 J. Peter Rosenfeld (ed.), Detecting Concealed Information and Deception: Recent Developments (2018).

13 Joseph R. Simpson (ed.), Neuroimaging in Forensic Psychiatry: From the Clinic to the Courtroom (2012).

14 Andrea L. Glenn & Adrian Raine, *Neurocriminology: Implications for the Punishment, Prediction and Prevention of Criminal Behaviour*, 15 Nat. Rev. Neurosci. 54 (2014); Eyal Aharoni et al., *Neuroprediction of Future Rearrest*, 110 PNAS 6223 (2013).

15 Farahany, *supra* note 1; De Kogel & Westgeest, *supra* note 1. See also Gerben Meynen, *Forensic Psychiatry and Neurolaw: Description, Developments, and Debates*, Int'l J.L. & Psychiatry, DOI: 10.1016/j.ijlp.2018.04.005 (2018); Henry T. Greely & Anthony D. Wagner, Reference Guide on Neuroscience, 798–99 (2011).

potential forensic applications of neuroimaging, are conceivable. A very interesting (relatively new) application is the use of neuroimaging together with machine-learning algorithms, which enables researchers to identify 'real-time thoughts' of an individual. Using this technology in a laboratory setting, researchers have been able to detect actual thoughts in real time about abstract physics concepts, and also identified suicidal thoughts with 91% accuracy.[16] Although this form of 'real-time neurotechnological mind reading' is still in its infancy, it may become a very valuable tool for future criminal investigators in determining whether a defendant has relevant knowledge about a specific crime.

Note that most of the neuroimaging applications discussed in this paper—especially real-time mind reading —are still in their experimental stages and therefore not ready for practical forensic use yet (although the results of some of these tests, like lie detection, have already been introduced, though rejected, as evidence, and memory detection has even already been used in a legal proceeding[17]). An important current limitation of lie and memory detection is, for example, that the subject can manipulate the scan results, using mental or physical countermeasures, such as moving his tongue or recalling emotional memories.[18] To some extent, this limitation applies to any neuroimaging application, since neuroimaging data are useless if the subject moves his head a few millimeters.[19] However, horizon scanning is an important task of neurolaw scholars in order to anticipate coming developments and consider potential legal implications of (coercive) neuroimaging in criminal law. It is important to do this before new technology actually arrives in court.[20]

When thinking about *coercive* neuroimaging, it is important to think about how different neuroimaging applications could be used effectively in a situation where coercion is applied to the suspect. Basically, there are two types of 'coercion' that may be used: physical and legal coercion.[21] In the context of *physical coercion*, a noncooperative or even resistant subject could be physically overpowered in order to enable a successful brain scan. For instance, a resistant subject might be physically secured in a way that makes movement impossible. In some cases, this could enable the examiner to accomplish a specific neuroimaging assessment.[22] Another possibility is the use of drugs that prevent movements for the purpose of carrying out the neuroexamination.

16 Robert A. Mason & Marcel A. Just, *Neural Representation of Physics Concepts*, 27 Psychol. Sci. 904 (2016); Marel A. Just et al., *Machine Learning of Representations of Suicide and Emotion Concepts Identifies Suicidal Youth*, 1 Nat. Hum. Behav. 911 (2017).

17 E.g. United States v. Semrau, 693 G.3d 510 (6th Cir. 2012); Larence A. Farwell, *Brain Fingerprinting: A Comprehensive Tutorial Review of Detection of Concealed Information with Event-Related Brain Potentials*, 6 Cogn. Neurodyn. 115, 131–32 (2012).

18 J. Peter Rosenfeld et al., *Simple, Effective Countermeasures to P300-Based Tests of Detection of Concealed Information*, 41 Psychophysiology 205 (2004); Anthony Wagner et al., *fMRI and Lie Detection: A Knowledge Brief of the MacArthur Foundation Research Network on Law and Neuroscience*, 3 (2016).

19 *Cf*. Nancy Kanwisher, *The Use of fMRI in Lie Detection: What Has Been Shown and What Has Not*, 12 in Using Imaging to Identify Deceit (Emilio Bizzi et al. eds, 2009).

20 Thomas Nadelhoffer & Walter Sinnott-Armstrong, *Neurolaw and Neuroprediction: Potential Promises and Perils*, 7 Philos. Compass. 631, 634 (2012).

21 Ligthart, *supra* note 10, at 89; Pardo & Patterson, *supra* note 4, at 153.

22 Ligthart, *supra* note 10; S. K. Thompson, *The Legality of the Use of Psychiatric Neuroimaging in Intelligence Interrogation*, 90 Cornell Law Rev. 1601, 1631 (2005).

Contrary to physical coercion, *legal coercion* does not imply any physical force in order to successfully accomplish a neuroimaging assessment. Instead, with legal coercion, the law threatens noncooperation with negative consequences for the subject, in order to make him *decide* to cooperate with a specific neuroimaging assessment. Such a legal threat could be direct (eg 'if you do not cooperate with test X, you will be punished', or 'if you do not cooperate with test X, adverse inferences might be drawn from your noncooperation') or rather indirect, formulated as an offer (eg 'you may be allowed out on parole, if you cooperate with test X').[23]

Regarding coercive neuroimaging in light of the right to privacy, the type of coercion that is used is relevant in two ways: practically and legally. The *practical relevance* is that some (functional) neuroimaging applications require the *active cooperation* of the subject.[24] For instance, in the context of brain-based lie detection, the subject has to perform a task by pressing a yes-or-no-button after each question. Furthermore, some types of brain-based memory detection, like the concealed information test, require the subject to *attentively* observe the presented stimuli.[25] In such cases, the use of physical force would probably be useless and would not assist in compelling a subject to perform a certain task, or to pay full attention to observing particular stimuli. Finally, as previously mentioned, the subject could influence the results of (most) neuroimaging applications through the use of countermeasures, like recalling emotional thoughts or moving his tongue. Physical coercion is, however, unlikely to prevent countermeasures like these.

The *legal relevance* of the distinction between physical and legal coercion is two-fold. Firstly, unlike legal coercion, physical coercion implies an (additional) interference with someone's (right to respect for) bodily integrity, which right is guaranteed by Article 8 ECHR.[26] Secondly, in the context of (indirect) legal coercion, the subject *decides* to cooperate with a certain neuroimaging application. Perhaps reluctantly he *consents* to it because, for instance, his cooperation will subsequently allow him to be released on parole. Free and informed consent to a particular governmental action removes state liability under specific European human rights, including Article 8 ECHR.[27] However, in the context of criminal justice, this may not always amount to *free* and informed consent. The circumstances when the right to respect for private life will be violated are discussed in the following section.

THE RIGHT TO PRIVACY AND ARTICLE 8 ECHR: A BRIEF INTRODUCTION

Article 8(1) ECHR states: 'Everyone has the right to respect for his private and family life, his home and his correspondence'. This paper only focuses on the right to respect

23 *Cf.* Jonathan Pugh, *Coercion and the Neurocorrective Offer*, in Treatment for Crime: Philosophical Essays on Neurointerventions in Criminal Justice (David Birks & Thomas Douglas eds., 2018).

24 Gerben Meynen, *Brain-Based Mind Reading in Forensic Psychiatry: Exploring Possibilities and Perils*, 4 J. Law Biosci. 311, 320 (2017).

25 J. Peter Rosenfeld et al, *The Complex Trial Protocol (CTP): A New, Countermeasure-Resistant, Accurate, P300-Based Method for Detection of Concealed Information,* 45 Psychophysiology, 906 (2008); Terence W. Piction, *The P300 Wave of the Human Event-Related Potential,* 9 J. Clin. Neurophysiol. 456, 459 (1992).

26 See Section 3 below.

27 Wannes Buelens, Coralie Herijgers & Steffi Illgems, *The View of the European Court of Human Rights on Competent Patients' Right of Informed Consent. Research in the Light of Article 3 and 8 of the European Convention on Human Rights,* 23 Eur. J. Health. Law. 481 (2016).

for private life. According to the Grand Chamber of the European Court on Human Rights (ECtHR), the notion of 'private life' within the meaning of Article 8 ECHR is a broad concept, which does not lend itself to exhaustive definition.[28] Since the ECtHR approaches the convention as a living instrument, which should be interpreted in light of the present-day conditions,[29] the meaning and scope of the notion of private life are continuously evolving, *inter alia* because of technological and social developments.

According to the Grand Chamber, personal autonomy is an important principle underlying the right to respect for private life.[30] In the same cases, the Court considers that it would be too restrictive to limit the notion of private life to an 'inner circle' in which the individual may live his own personal life as he chooses, but it also includes the right to lead a private social life, ie the possibility for an individual to develop his social identity.

Although the precise meaning and scope of the right to respect for private life are not fixed, it is clear that it covers the right to respect for physical and psychological integrity[31] and the protection of personal data.[32] In determining whether certain information recorded and retained by the authorities involves any of the protected private-life aspects, the ECtHR will have due regard to the specific context in which the information at issue has been recorded and retained, the nature of the records, the way in which these records are used and processed, and the results that may be obtained.[33] In any event, information relating to an identified or identifiable individual (personal data) falls within the scope of the right to respect for private life.[34]

Besides events within someone's private area, like one's home, the right to respect for private life offers, under certain circumstances, protection outside such private areas. A significant, but not necessarily conclusive, factor in this respect is the reasonable expectation of privacy of the person concerned.[35] Note, however, that the way in which the ECtHR applies the reasonable-expectation-of-privacy test differs from the way in which the Supreme Court of the USA considers privacy. Unlike Article 8 ECHR, the Fourth Amendment of the Bill of Rights only offers protection against searches if the person concerned has a subjective expectation of privacy that society recognizes to be reasonable.[36] In order to *restrict* the scope of the Fourth Amendment, it *only* protects those situations in which a person may have a reasonable expectation of his

28 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 159 (January 24, 2017); ECtHR (GC) Aksu v. Turkey, appl.nos. 4149/04 and 41029/04, § 58 (March 15, 2012).

29 ECtHR Tyrer v. UK, appl.no. 5856/72, § 31 (April 25, 1978).

30 ECtHR (GC) Bărbulescu v. Romania, appl.no. 61496/08, § 70 (September 5, 2017); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 66 (December 4, 2008).

31 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 159 (January 24, 2017); ECtHR (GC) Bédat v. Switzerland, appl.no. 56925/08, § 72 (March 29, 2016).

32 ECtHR (GC) Magyar Helsinki Bizottság v. Hungary, appl.no. 18030/11, § 191 (November 8, 2016); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 66–67 (December 4, 2008).

33 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 66 (December 4, 2008); Karin de Vries, *Right to Respect for Private and Family Life,* in Theory and Practice of the European Convention on Human Rights 673 (Pieter van Dijk et al. eds. 2018).

34 ECtHR (GC) Amann v. Switzerland, appl.no. 27798/95, § 65–67 (February 16, 2000); ECtHR (GC) Rotaru v. Romania, appl.no. 28341/95, § 43 (May 4, 2000).

35 ECtHR (GC) Bărbulescu v. Romania, appl.no. 61496/08, § 73 (September 5, 2017); ECtHR Uzun v. Germany, appl.no. 35623/05, § 44, 47 (September 2, 2010).

36 Smith v. Maryland, 442 U.S. 735 (1979), 735, 740–41. See also Farahany, *supra* note 4, at 1256–49.

privacy. Contrary to the Supreme Court of the USA, the ECtHR applies the reasonable-expectation-of-privacy test in order to *broaden* the scope of the right to privacy. Many aspects of someone's life are so private that they a priori fall within the scope of the right to respect for private life, including the right to respect for physical integrity, personal data, and the right to respect for the decisions both to have and not to have a child.[37] Furthermore, even if the private nature of, for example, certain information is not crystal clear, the ECtHR is willing to accept protection of the right to respect for private life, if one has a reasonable expectation of one's privacy. Privacy protection has for instance been acknowledged regarding secretly taking of footage of a defendant within a police station for the purposes of video identification, because the defendant did not have any expectation that such footage was being taken.[38]

If the government interferes with someone's protected private interests, the right to respect for private life will not necessarily be violated. According to Article 8(2) of the ECHR, interferences can be justified if they are in accordance with the (rule of) law and necessary in a democratic society in the legitimate interest of: national security, public safety or the economic well-being of the country, the prevention of disorder or crime, the protection of health or morals, or the protection of the rights and freedoms of others.[39]

Prior to applying the right to respect for private life to coercive neuroimaging in criminal law, what follows draws an analogy between coercive forensic neuroimaging on the one hand and, on the other hand, research methods about which case law of the ECtHR already exists, regarding rights protected by Article 8 ECHR.

AN ANALOGY: DNA AND FINGERPRINTS

As yet, there is no ECtHR case law regarding the use of coercive neuroimaging in criminal law. Therefore, it will be helpful to compare coercive forensic neuroimaging with other methods of criminal investigation, about which case law does already exist.[40] This case law about comparable methods can provide interesting insights into how we could, or, should, approach the use of coercive forensic neuroimaging in light of the right to respect for private life.

It has already been stated that neuroimaging applications acquire brain-related *information* of an individual that could assist in answering legal questions, relevant to guilt, legal insanity, fitness to plead, and recidivism risks. As mentioned earlier, the state's acquisition, retention, and use of information about an individual may fall within the scope of Article 8 ECHR. In establishing whether this is the case, the court will have due regard to the following (these are paraphrased) factors:

I. The nature of the information and the results that may be obtained
II. The specific context in which the information has been recorded and retained, and

37 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 159 (January 24, 2017).
38 ECtHR Perry v. UK, appl.no. 63737/00, § 40–41 (July 17, 2003).
39 On this topic see David J. Harris et al., Harris, O'Boyle, and Warbrick Law of The European Convention on Human Rights 505 et seq. (2014).
40 Ligthart, *supra* note 10, at 94.

III. The way in which the information is used and processed.[41]

In this section, I argue that, in light of these three relevant aspects in the context of Article 8 ECHR, coercive neuroimaging is comparable to the compulsory taking and retaining of DNA and fingerprints. Not in the sense that they are completely similar, but that they have sufficient relevant similarities to take case law on DNA and fingerprints into account in the examination of the legal implications of coercive neuroimaging in light of Article 8 ECHR. However, there are also significant differences to which I will pay particular attention in Section 5.

I. The nature and possible results of the information. According to the Grand Chamber, a notable characteristic for DNA and fingerprints is that they contain unique data about an individual, which allows for identification.[42] This is because the information relates to an identified or identifiable individual; thus, DNA and fingerprints contain personal data.[43]

Just like DNA and fingerprints, brain anatomy and activity also relate to an identified individual (to the person who is subjected to a neuroimaging assessment). Therefore, the results of structural and functional neuroimaging must also constitute personal data. Furthermore, similar to DNA and fingerprints, the anatomy of a person's brain is arguably unique, since even the brains of monozygotic twins appear to be not identical.[44] In addition, research regarding 'brain printing' shows that brain activity (more specifically: functional brain connectivity) is also unique for any individual, just like a fingerprint.[45] For instance, as Finn et al. wrote in *Nature Neuroscience*:

> Here, we show that an individual's functional brain connectivity profile is both unique and reliable, similarly to a fingerprint. We demonstrate that it is possible, with near-perfect accuracy in many cases, to identify an individual from a large group of subjects solely on the basis of his or her connectivity matrix.[46]

So, DNA, fingerprints, and brain anatomy and activity are unique and personal. Furthermore, they are all biological in nature: they concern human characteristics and/or reactions, like the structure of someone's fingertip, the structure of one's brain, DNA in saliva or blood, hemodynamics in blood, and brain electricity. Accordingly, it is reasonable to assume that the ECtHR would find that neuroimaging data of this type constitute personal data.

Furthermore, the results that may be obtained from DNA and fingerprints may be used in the future to demonstrate information about someone's involvement, or future

41 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 67 (December 4, 2008); De Vries *supra* note 33, at 673.

42 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 72, 75, 84 (December 4, 2008); ECtHR Aycaguer v. France, appl.no. 8806/12, § 33 (June 22, 2017).

43 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 68 (December 4, 2008).

44 Alexander Mohr et al., *The Similarity of Brain Morphology in Healthy Monozygotic Twins*, 20 Cogn. Brain. Res. 106 (2004).

45 E.g. E. S. Finn et al., *Functional Connectome Fingerprinting: Identifying Individuals Using Patterns of Brain Connectivity,* 18 Nat. Neurosci. 1664, (2015); L. Waller et al., *Evaluating the Replicability, Specificity, and Generalizability of Connectome Fingerprints*, 158 Neuroimage. 371 (2017); Ienca & Andorno, *supra* note 7, at 14; Farahany, *supra* note 4, at 1281.

46 Finn et al., *supra* note 45, at 1669.

involvement, in a crime.[47] While the original taking of DNA and fingerprints pursues the aim of linking a particular person to the particular crime of which he is suspected, their retention pursues the broader purpose of assisting in the identification of future offenders.[48] The same applies *mutatis mutandis* to coercive forensic neuroimaging. In a criminal law context, brain-based lie and memory detection, as well as diagnostic neuroimaging, aim to contribute to answering questions regarding the subject's criminal responsibility, while neuroprediction helps identify the likelihood of future offending. Altogether, the nature and possible results of the information obtained with fingerprinting and DNA testing are in a relevant way comparable to those of coercive neuroimaging in criminal law.

II and III. The context and possible use of the information. Just like DNA testing and fingerprinting, coercive forensic neuroimaging will be used in the context of the criminal law.[49] The possible use of the information yielded through these tests is also similar. According to the ECtHR, the information obtained with fingerprinting and DNA testing can be used against the person concerned, but he can also reap a certain benefit from it: DNA and fingerprints also allow for the rapid elimination of a person identified as a possible suspect of a particular crime in the investigation of which DNA or fingerprints have been found.[50] This is also true for neuroimaging in criminal law. On the one hand, neuroimaging applications can contribute in the determination of a defendant's guilt, legal responsibility, and risk of recidivism, but, on the other hand, a defendant or prisoner can also *request*, for example, a brain-based memory detection or a diagnostic brain scan, in order to strengthen his statement of not knowing anything about the crime he is suspected of, or to support his claim of legal insanity.[51]

In sum, the nature, context and possible use of DNA and fingerprints are, to a relevant extent, comparable to those of the forensic neuroimaging. This enables us to compare these methods in more detail in the following section in light of case law regarding the right to respect for private life as developed through Article 8 ECHR.

AN ANALYSIS: COERCIVE FORENSIC NEUROIMAGING IN LIGHT OF THE RIGHT TO PRIVACY

INTRODUCTION

This section examines the main question of this paper: how does coercive neuroimaging in criminal law relate to the right to respect for private life as laid down in Article 8 ECHR? First, in Section 5.2, I explain how coercive neuroimaging interferes with the right to respect for private life (Article 8(1) ECHR). Subsequently, in Section 5.3, I argue that the (potential) interferences made by most neuroimaging applications can,

47 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 100, 105 (December 4, 2008); ECtHR Peruzzo and Martens v. Germany, appl.nos. 7841/08, 57900/12, § 40 (June 4, 2013).

48 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 100 (December 4, 2008).

49 For DNA and fingerprinting in this context see e.g. ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04 (December 4, 2008); ECtHR Caruana v. Malta, appl.no. 41079/16 (May 15, 2018); ECtHR Peruzzo and Martens v. Germany, appl.nos. 7841/08, 57900/12 (June 4, 2013); ECtHR W. v. The Netherlands, appl.no. 20689/08, (January 20, 2009); ECtHR Van der Velden v. The Netherlands, appl.no. 29514/05 (December 7, 2006); ECtHR Schmidt v. Germany, appl.no. 2352/02 (January 5, 2006).

50 ECtHR W. v. The Netherlands, appl.no. 20689/08, 8 (January 20, 2009).

51 Meynen *supra* note 15, at 3.

probably, be justified (using the qualifications to the right contained in Article 8(2) ECHR).

The premise of this analysis is the analogy between compulsory fingerprinting and DNA testing on the one hand and coercive forensic neuroimaging on the other hand. Based on similarities—but also on important differences—I will draw together relevant insights from case law regarding DNA and fingerprints to understand the way in which we could approach coercive forensic neuroimaging in light of the right to privacy.

HOW COERCIVE NEUROIMAGING INTERFERES WITH THE RIGHT TO PRIVACY

In contrast with the reasonable-expectation-of-privacy test employed in the US legal context,[52] in the European approach, this test is superfluous in examining whether and how coercive neuroimaging interferes with the right to respect for private life contained in Article 8 ECHR. As discussed in Section 3, the right to privacy as guaranteed by Article 8 ECHR directly protects someone's physical and psychological integrity and his personal data. As I argue below, coercive neuroimaging interferes with both of these rights.

Firstly, according to the ECtHR, a person's body concerns the most intimate aspect of private life; any medical intervention against someone's will—even if it is a minor interference—such as compulsory taking blood, saliva or urine, constitutes an interference with the right to respect for physical integrity and thus with the right to respect for private life.[53] Just like DNA testing,[54] neuroimaging is, basically, a medical procedure, that is commonly used in medical practice, for instance to locate a tumor (MRI), acquire information about bone fractures (CT), or to diagnose epilepsy (EEG).[55] Therefore, applying neuroimaging with coercion—so against the will of the subject—constitutes an interference with the subject's right to respect for private life, as would a compulsory X-ray screening for tuberculosis.[56] If the authorities use *physical coercion* in order to obtain a specific neuroimage, an additional interference will occur with the subject's right to physical integrity and thus with his right to respect for private life.[57]

Secondly, the Grand Chamber has found the protection of personal data to be of fundamental importance to a person's enjoyment of his right to respect for private life. Thus, the compulsory taking, retaining, and/or using of someone's personal data, like DNA or fingerprints interferes with the right to respect for personal data and thus

52 See *i.a.* Pardo & Patterson, *supra* note 4, at 153–54; Shen *supra* note 4, at 699; Madison Kilbride & Jason Iuliano, *Neuro Lie Detection and Mental Privacy*, 75, MD. L. Rev. 163, 192 (2015); John B. Meixner Jr., *Admissibility and Constitutional Issues of the Concealed Information Test in American Courts: An Update,* in Detecting Concealed Information and Deception: Recent Developments 423 (J. Peter Rosenfeld ed., 2018); Benjamin Holley, *It's All in Your Head: Neurotechnological Lie Detection and the Fourth and Fifth Amendments*, 28 Dev. Mental Health L. 12–3 (2009).

53 ECtHR Yuriy Volkov v. Ukrain, appl.no. 45872/06, § 84 (December 19, 2013); ECtHR Caruana v. Malta, appl.no. 41079/16, § 26 (May 15, 2018); ECtHR Schmidt v. Germany, appl.no. 2352/02, § 4 (January 5, 2006); ECtHR Young v. UK, appl.no. 60682/00, § 12 (October 11, 2005).

54 ECtHR Jäggi v. Switzerland, appl.no. 58757/00, § 38 (July 13, 2006).

55 *Cf.* Greely & Wagner *supra* note 15, at 763–65, 768, 772.

56 ECHR Acmanne and others v. Belgium, appl.no. 10435/83 (December 10, 1984).

57 *Cf.* ECtHR Coman v. Romania, appl.no. 29106/13, § 38–42 (May 31, 2016).

with the right to respect for private life.[58] As we saw in Section 4, neuroimaging results contain personal data. Therefore, obtaining (retaining and using) those results against a person's will through coercive neuroimaging also constitutes an interference with the right to respect for private life.

So, in short, coercive neuroimaging in criminal law interferes with the right to respect for private life in two ways: through an interference with (i) the subject's bodily integrity and (ii) his personal data. But potentially unlawful interferences will only occur if the neuroimaging is carried out without the subject's consent. It is because coercive neuroimaging is a medical procedure that yields personal information, and it is used *against the will of the subject*, that it interferes with the right to respect for private life. This is because, according to the ECtHR, 'Any medical intervention against the subject's will or without the free, informed, and express consent of the subject constitutes an interference with his or her private life'.[59]

Interesting, in this regard, is that a medical intervention that is applied *with* the subject's free, informed, and express consent will normally *not* interfere with the subject's right to respect for private life.[60] Regarding forensic neuroimaging, however, the question arises whether and, if so, under which conditions consent for a particular neuroimaging application could be considered to be free, since refusing cooperation with neuroimaging could in some cases have (indirect) negative legal implications for the subject. For example, if for a successful parole request, the results from a recent neuroprediction test are a prerequisite; in such a case, the prisoner who wants parole could feel pressured to give his consent and cooperate 'willingly' with a neuroprediction assessment. In cases like this, however, the question arises whether consent given under such a kind of indirect legal pressure can be considered to be free or whether such pressure will invalidate (the voluntariness of) the consent. Examining this question requires an in-depth analysis of the philosophical and legal principle of informed consent, as well as the case law of the ECtHR in which the validity of informed consent has been at stake. While in my view, it can be argued both from a legal and philosophical perspective that in cases of imbalance of power and dependency, like in prison, the voluntariness of consenting decisions should be examined closely, further examination of this question is beyond the scope of this paper.[61]

WHETHER COERCIVE NEUROIMAGING COULD BE JUSTIFIED

As was briefly mentioned in Section 3, an *interference* with the right to respect for private life will not necessarily imply a *violation* of this right. According to Article 8(2) ECHR,

58 ECtHR Peruzzo and Martens v. Germany, appl.nos. 7841/08, 57900/12, § 33 (June 4, 2013); ECtHR M.K. v. France, appl.no. 19522/09, § 29 (April 18, 2013); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 67, 77, 86 (December 4, 2008).

59 ECtHR Juhnke v. Turkey, appl.no. 52515/99, § 76 (May 13, 2008). See also ECtHR Atudorei v. Romania, appl.no. 50131/08, § 161–64 (September 16, 2014); Buelens, Herijgers & Illegems, *supra* note 27.

60 Which is even true in the context of the absolute prohibition of ill-treatment, in which context the ECtHR has stated that, if there is informed consent for a medical procedure, no issues arises under this prohibition (ECtHR Bogumil v. Portugal, appl.no. 35228/03, § 71 (October 3, 2008). See Ligthart *supra* note 10.

61 For this discussion see *i.a.* Pugh *supra* note 23; Sjors Ligthart, *Coercive Forensic Neuroimaging and the Prohibition of Ill-treatment (article 3 ECHR)*, in Law, Science and Rationality (Anotonia M. Walterman, David Roef, Jaap Hage & Marko Jelicic, forthcoming).

such an interference can be justified if it (i) is in accordance with the law, (ii) serves a legitimate interest, and (iii) is necessary in a democratic society.

If the government develops sound legislation based on which coercive neuroimaging can be applied in criminal justice, in the legitimate interest of national security, the detection and prevention of crime, or the protection of the rights and freedoms of others, the first two requirements to justify an interference with the right to respect for private life are unlikely to give rise to much discussion.

The third requirement—whether the interference is necessary in a democratic society—is more open for debate. According to the ECtHR, an interference can be necessary if it corresponds to a pressing social need and, in particular, if it is proportionate to the legitimate interest pursued.[62] In this regard, the Court takes into account whether the reasons adduced to justify a particular measure are relevant and sufficient for the legitimate interest that the measure serves.[63] Ultimately, a 'fair balance' has to be struck between the competing interests of the individual on the one hand and of society on the other hand.[64]

In determining a fair balance and the necessity of an interference with the right to respect for private life, the ECtHR takes into account that a 'margin of appreciation' is left to the national authorities. The broader this margin, the more discretion States have in finding a fair balance between the competing interests at stake. The breadth of the margin of appreciation depends on a number of relevant circumstances, including the nature of the human right in issue and the nature and purpose of the interference.[65] If the right in issue is crucial to the individual's effective enjoyment of intimate or key rights, such as the right to personal autonomy, or, if another, particularly important facet of an individual's existence, or identity is at stake, the margin of appreciation allowed to the State will normally be restricted.[66] On the other hand, if there is no consensus within the member States of the Council of Europe, either as to the relative importance of the interest in issue or as to the best way of protecting it—particularly where the case raises sensitive moral or ethical issues—the margin will be wider.[67] So in sum, whether coercive neuroimaging in criminal law is necessary in a democratic society depends on whether it corresponds to a pressing social need and is proportionate with the aims pursued. This will be assessed within the margin of appreciation that is afforded to the member States. These three factors - margin of appreciation, pressing social need and proportionality - are discussed below regarding coercive forensic neuroimaging.

I. The margin of appreciation. In the investigation, punishment and prevention of crime, the member States of the Council of Europe are entitled to a certain

62 ECtHR (GC) Khoroshenko v. Russia, appl.no 41418/04, § 118 (June 30, 2015); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 101 (December 4, 2008).

63 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 179 (January 24, 2017); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 101 (December 4, 2008).

64 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 181 (January 24, 2017); ECtHR (GC) A, B and C v. Ireland, appl.no. 25579/05, § 229 (December 16, 2010).

65 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 102 (December 4, 2008).

66 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 102 (December 4, 2008); ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 182 (January 24, 2017).

67 ECtHR (GC) Paradiso and Campanelli v. Italy, appl.no. 25358/12, § 182 (January 24, 2017); ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 102 (December 4, 2008).

margin of appreciation.[68] However, since the discussion about the legal implications of (coercive) neuroimaging in criminal justice in Europe is still in its infant stage, there is no, as yet, consensus as to how to regulate the coercive use of these technologies in criminal law. Moreover, besides the lack of consensus regarding the possible *legal* implications, coercive forensic neuroimaging also raises important *ethical* and *moral* (privacy) issues, which are currently being debated.[69] These two elements—the lack of legal consensus and the ethical and moral sensitivity of coercive neuroimaging—suggest that the ECtHR might advocate a wider margin of appreciation for States that want to implement coercive neuroimaging in their criminal legal systems. However, in a landmark case concerning forensic DNA testing, the Grand Chamber considered that:

> The protection afforded by Article 8 of the Convention would be unacceptably weakened if the use of modern scientific techniques in the criminal-justice system were allowed at any cost and without carefully balancing the potential benefits of the extensive use of such techniques against important private-life interests. (. . .) The Court considers that any State claiming a pioneer role in the development of new technologies bears special responsibility for striking the right balance in this regard.[70]

So, where the ethical and moral sensitivity and the lack of legal consensus on the one hand might argue for a wider margin of appreciation, being a pioneer in applying coercive neuroimaging seems on the other hand also to narrow that margin. From a historical perspective, it is understandable that the ECtHR underlines the importance of cautiousness in introducing new technologies that yield personal information about civilians for purposes of criminal justice. After all, during the Second world war, and also during the *Stasi* regime in East Germany—only 35 years ago—certain thoughts and beliefs could have far-reaching negative consequences for individual civilians.

One could, however, argue that the use of some neuroimaging technologies in criminal law is not reserved for pioneering European countries anymore, since particular (mostly structural) neuroimaging technologies have already entered the criminal courtrooms of, *inter alia*, Slovenia, England and Wales, and the Netherlands. Although some neuroimaging technologies are indeed already being used in different criminal justice systems within Europe, yet there is no evidence that these technologies are applied with coercion. Therefore, being a pioneer in the use of *coercive* forensic neuroimaging will most probably restrict the margin of appreciation of the concerned State.

Besides the ethical and moral debates and the lack of legal consensus, the breadth of the margin of appreciation may be influenced by the nature of the right at stake. Thus, if coercive forensic neuroimaging interferes with the subject's effective enjoyment of intimate or key rights, or with another particularly important facet of his existence or identity, the margin of appreciation will be relatively small. As discussed in Section 4, coercive neuroimaging in criminal law interferes with the right to respect for privacy in two ways: through an interference with (i) the subject's physical integrity and (ii) his

68 ECtHR Klass and others v. Germany, appl.no. 5029/71, § 49 (September 6, 1978); ECtHR (GC) Murray v. UK, appl.no. 14310/88, § 90 (October 28, 1994).

69 Jesper Ryberg, *Neuroethics and Brain Privacy: Setting the Stage*, 23 Res. Publica. 153 (2017); Meynen *supra* note 15; Adina L. Roskies, *Mind Reading, Lie Detection, and Privacy*, in Handbook of Neuroethics 679–95 (Jens Clausen & Neil Levy eds., 2015).

70 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 112 (December 4, 2008).

personal data. However, using neuroimaging against someone's will in order to examine whether, for instance, a defendant answers a *specific* question truthfully, or whether he recognizes a *particular* object (like a gun) does not, in my view, interfere with an intimate or key right, nor with any important facet of someone's existence or identity. Therefore, the margin of appreciation within which States may balance the competing interests of coercive forensic neuroimaging should not be restricted.

It could be argued that some coercive neuroimaging applications, such as memory detection with the concealed information test, do interfere with a key or intimate right, namely with the right to personal autonomy.[71] The line of argument then is more or less the following. Memories are shielded from the outside world in such a way that, when they are not revealed by the person himself, others can never take cognizance of them. In addition, memories are an important part of someone's personal identity, because based on their experiences people continue or adapt their behavior and shape their identity. Any infringement with someone's autonomy to disclose his memories (or other thoughts) constitutes an interference with an intrinsic component of one's personality: if undisclosed, personal information is no longer separable, the right to privacy becomes illusory. Since brain-based mind reading is a method, which can reveal undisclosed information regarding someone's thoughts or memories, the margin of appreciation, in this regard, should be restricted.[72]

This line of argument seems to presuppose that neuroimaging applications, such as memory detection, extract a whole bunch of memories about all kind of experiences the subject has had so far. However, this is not very likely. Neuroimaging applications, which can, in a certain way, yield information regarding someone's thoughts or memories, such as brain-based lie and memory detection, only enable the examiner to detect some *specific* lies or memories regarding a *specific* event, such as a *particular* crime. Whether a defendant *recognizes* some particular objects, like a gun, getaway car, and sports bag, is, in general, not significant for his personal identity. Notice, however, that some neuroimaging applications can yield intimate information about someone's identity, eg regarding sexual preferences, which is relevant in the context of whether coercive neuroimaging application is proportionate (see point III below). However, in my view, *detecting* such information does not per se interfere with the subject's personal autonomy, which the ECtHR has defined as 'the right to make choices as to how to lead one's own life'.[73] In contrast, cases in which personal autonomy has been at stake have concerned topics like abortion, voluntary euthanasia, and recognition of transsexuals.[74]

Furthermore, it is questionable whether neuroimaging applications are indeed the only methods that can yield undisclosed personal information.[75] Such undisclosed

71 Andrea Lavazza, *Freedom of Thought and Mental Integrity: The Moral Requirements for Any Neural Prosthesis*, 12 Front Neurosci. 4 (2018); Van Toor *supra* note 6, at 298, 363–67.

72 Van Toor *supra* note 6, at 298, 363–67. *Cf.* Andrea Lavazza, *Freedom of Thought and Mental Integrity: The Moral Requirements for Any Neural Prosthesis*, 12 Front Neurosci. 4 (2018); Nita A. Farahany, *Incriminating Thoughts*, 64 Stan. L. Rev. 351, 406 (2012).

73 ECtHR M. and M. v. Croatia, appl.no. 10161/13, § 171 (September 3, 2015).

74 ECtHR (GC) A, B and C v. Ireland, appl.no. 25579/05, § 216 (December 16, 2010); ECtHR Pretty v. UK, appl.no. 2346/02, § 61–67 (April 29, 2002); ECtHR I./UK, appl.no. 25680/94, § 70–73 (July 11, 2002).

75 Moreover, one could also doubt whether neuroimaging indeed yields *undisclosed* information since thoughts, moods and emotions are also expressed by the way in which a person looks, reacts and behaves: Jesper Ryberg, *Neuroscience, Mind Reading and Mental Privacy*, 23 Res. Publica. 197, 206, 209 (2017).

information can, for instance, also be obtained through a compulsory blood alcohol test. This is because nobody knows how many beers a particular person drank during the time he was home alone, prior to driving—except for the person himself. If someone suspected of impaired driving does not disclose any information about his alcohol consumption by for example remaining silent and refusing to supply breath for a breathalyzer test, the undisclosed information can nevertheless be revealed by the authorities through a compulsory blood alcohol test. The fact that such a blood test reveals undisclosed information has not been held to contravene the right to respect for private life contained within Article 8 ECHR.[76] Blood alcohol tests do not interfere with a person's right to personal autonomy, ie with a person's right to make choices as to how to lead one's own life. The mere obligation to supply a small amount of blood, urine or saliva, or to cooperate with a single MRI or EEG scan does in principle not restrict a person in making choices about how to lead his life.[77]

Altogether, coercive forensic neuroimaging does not, in my view, interfere with any key right or other important facet of someone's existence or identity. Accordingly, the margin of appreciation afforded to participating States should not be restricted in this way. Furthermore, the ethical and moral sensitivity of coercive forensic neuroimaging and the lack of legal consensus, together with the aims of coercive neuroimaging, advocate a wider margin of appreciation. This margin, however, finds its limits in the statement of the ECtHR that any State claiming a pioneer role in the development of new technologies bears special responsibility for striking the right balance. However, the extent to which this special responsibility restricts the margin of appreciation for the use of coercive neuroimaging is hard to predict.

II. A pressing social need. To be necessary in a democratic society, coercive forensic neuroimaging should, within the margin of appreciation, correspond to a pressing social need. This requirement should not be very problematic for the use of coercive neuroimaging, since the Grand Chamber finds the application of new technologies, for example in the context of DNA testing, essential in the fight against crime:

> The Court finds it to be beyond dispute that the fight against crime, and in particular against organized crime and terrorism, which is one of the challenges faced by today's European societies, depends to a great extent on the use of modern scientific techniques of investigation and identification.

Especially with current levels of terrorism threat, the use of new technologies such as coercive neuroimaging will probably correspond to the pressing social needs of protecting national security and preventing (serious) crime and public disorder.

III. Proportionality. Finally, an interference in someone's right to respect for private life caused by a coercive neuroimaging application, has to be proportionate with the legitimate aim pursued in order to be recognized by the ECtHR as justified. Whether a

76 ECtHR Tirado Ortiz and Lozano Martin/Spain, appl.no. 43486/98 (June 15, 1999); ECHR X. v. The Netherlands, appl.no. 8239/78 (December 4, 1978).

77 This could be different though regarding compulsory neuroenhancement: Jan Christoph Bublitz, "*The Soul is in the Prison of the Body"—Mandatory Moral Enhancement, Punishment & Rights against Neuro-rehabilitation*, in Treatment for Crime: Philosophical Essays on Neurointerventions in Criminal Justice 302 (David Birks & Thomas Douglas eds. 2018).

specific coercive neuroimaging assessment will be proportionate, will depend on the circumstances of the particular case. Nevertheless, some general statements can be made in this regard.

In order to examine whether a fair balance has been struck between an interference with someone's right to respect for private life on the one hand, and the aim of that interference on the other, the ECtHR will determine the seriousness of the interferences made through coercive neuroimaging. As discussed in Section 4, coercive neuroimaging interferes with the subject's physical integrity and with his right to respect for personal data. The seriousness of both interferences is discussed below.

In the context of compulsory DNA testing through taking blood and saliva, the ECtHR considers that such methods are of very short duration, usually causes no bodily injury or any physical or mental suffering. Therefore, the interferences with the subject's physical integrity made through these compulsory methods are, according to the ECtHR, of 'minor importance' and 'relatively slight'.[78] Although a neuroimaging assessment usually takes longer than obtaining a blood sample, it normally causes no bodily injury nor mental suffering (except in specific cases where eg a pregnant or claustrophobic person is coerced to undergo a CT or fMRI scan). Some neuroimaging techniques do require injection of contrast liquid into the bloodstream of the subject, which is physically intrusive. However, although *injecting* contrast liquid may be more intrusive than *obtaining* a blood sample, such an injection does not constitute, in my view, a significantly more serious interference with someone's physical integrity than a compulsory blood test. So, because (coercive) neuroimaging usually causes no bodily injury nor any physical or mental suffering, the interference with the subject's physical integrity might, in the eyes of the ECtHR, be relatively slight and of minor importance. This could of course be different if the authorities use physical or chemical coercion in order to apply a particular neuroimaging application.[79]

The seriousness of the interference with the right to respect for personal data, respecting the collection and retention of personal data, like cellular material, DNA profiles, and fingerprints, depends on the sensitivity of the particular data in issue.[80] For instance, according to the Grand Chamber, cellular material is of a highly personal nature, contains much sensitive information about an individual, including information about the person's health, and contains a unique genetic code of great relevance to both the individual and his relatives.[81] Additionally:

> bearing in mind the rapid pace of developments in the field of genetics and information technology, the Court cannot discount the possibility that in the future the private-life interests bound up with genetic information may be adversely affected in novel ways or in a manner, which cannot be anticipated with precision today.[82]

78 ECtHR Van der Velden v. The Netherlands, appl.no. 29514/05, § 9 (December 7, 2006); ECtHR Caruana v. Malta, appl.no. 41079/16 (May 15, 2018); ECtHR Schmidt v. Germany, appl.no. 2352/02, § 4–5 (January 5, 2006).

79 See Ligthart *supra* note 10.

80 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 86, 120 (December 4, 2008).

81 *Id.* at § 72. That only a limited part of this information is actually extracted or used by the authorities through DNA profiling and that no immediate detriment is caused in a particular case does, according to the Court, not change this view (§ 73).

82 *Id.* at § 71. In this regard, we could for instance think of the possible predictive value of genetics in the context of criminal justice: Glenn & Raine *supra* note 14; Daniel R. Rosell & Larry J. Siever, *The Neurobiology of*

The ECtHR has been firm in stating that although DNA profiles contain a more limited amount of personal information than cellular material, the profiles do contain substantial amounts of unique personal data. In this regard, the Court notes that DNA profiles contain sensitive information about a person's ethnic origin and could be used for familial searching with a view to identifying a possible genetic relationship between individuals.[83] Following the Court's reasoning, fingerprints contain the least sensitive data in this respect, but nevertheless are protected by Article 8 ECHR since they contain unique information about an individual, allowing for his identification.[84]

The privacy sensitivity of the results of different neuroimaging applications is also distinctive. This has similarities with the results of fingerprinting and DNA testing. Most sensitive in this regard are probably the results of diagnostic neuroimaging. Just like current methods of diagnostics, diagnostic neuroimaging yields information that contains information regarding someone's (mental) health. In the view of the ECtHR, such information 'by its very nature constitutes highly sensitive personal data regardless of whether it was indicative of a particular medical diagnosis'.[85] If a specific diagnosis focusses on a sexual disorder, like paraphilia, the results will be even more sensitive in terms of privacy, since, according to the Court, someone's sexual interests concern a most intimate aspect of private life.[86] Additionally, it is not possible to discount the possibility that in the future, the privacy interests bound up with the results of diagnostic neuroimaging may be adversely affected in novel ways or in a manner, which cannot be anticipated with precision today in view of the developments in neuroprediction and brain printing.[87]

Secondly, similar to current risk assessment tools, neuroprediction could contribute to predicting somebody's behavior and his risk of criminal offending. Although the individual himself may not be aware of the information, which is yielded in this context,[88] the results of neuroprediction are quite sensitive in terms of privacy. After all, disclosing someone's (brain-based) risk to criminal offending, for instance through a legal verdict, could have far-reaching consequences for the person involved. Evidence as to the risk of future offending, or even of future arrest,[89] could for instance be problematic in the context of a job application or mortgage request.

Similar to diagnostic neuroimaging, the privacy sensitivity of the results of neuroprediction will increase if they relate to the subject's sexual life, such as the risk of child molestation or bestiality. The sensitivity of the yielded information will also increase if it (unforeseeably) contains information regarding the subject's health, for instance

Aggression and Violence, 20 CNS Spectrums. 254 (2015); Hannah L. Bedard, *The Potential for Bioprediction in Criminal Law* XVIII, Colum. Sci. & Tech. L. Rev. 268 (2017).

83 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 74–76 (December 4, 2008).

84 *Id*. at § 84.

85 ECtHR Surikov v. Ukraine, appl.no. 42788/06, § 75 (January 26, 2017); ECtHR Mockutė v. Lithuania, appl.no. 66490/09, § 94 (February 27, 2018).

86 ECtHR Dudgeon v. UK, appl.no. 7525/76), § 52 (October 22, 1981); ECtHR Stübing v. Germany, appl.no. 43547/08, § 59 (April 12, 2012).

87 *Supra* note 14, 44 and 45.

88 Meynen *supra* note 15, at 319.

89 Aharoni et al. *supra* note 14.

because the imaging results unexpectedly show the presence of a brain tumor.[90] As with diagnostic neuroimaging, we cannot discount the possibility that brain activity, which is measured in the context of neuroprediction, could in the future also be used for biometric identification of the person involved.

Finally, brain-based lie and memory detection, in general, probably yield the least sensitive information. Similar to fingerprinting and a blood alcohol test, the information acquired with memory and lie detection does not normally concern a sensitive area of someone's private life, but only relates to one specific, criminally relevant past event or act of the person concerned, on which the examination focusses (eg whether a defendant has been on a particular place, consumed alcohol before driving, recognizes a specific hammer, or was indeed visiting his parents at the time of a particular crime). Whether someone recognizes a specific object or visited his parents, is, in my view, not very sensitive in terms of privacy. Furthermore, contrary to, for instance, the neuroimaging results of neuroprediction and DNA testing, which can also be relevant in the context of a future job application or the determination of familial connections, the results of lie and memory detection are in principle only relevant within the context of a particular criminal procedure.

Ultimately, however, the sensitivity of the results will depend on the circumstances of a particular case. Applying brain-based lie detection in order to examine whether a sex offender watched child pornography during his probation, for instance, yields sensitive information regarding the subject's sexual life. Furthermore, brain-based lie and memory detection in the context of forensic diagnostics yield sensitive information regarding the subject's health. Such information could also be gathered unexpectedly, for instance if the fMRI results suggest that the subject suffers from a tumor or traumatic brain injury. Finally, the results of brain-based lie and memory detection could potentially be subjected to future scientific interpretation and could therefore affect the subject's privacy interests in a way that is not foreseeable.[91]

In sum, the privacy sensitivity of the results of the four neuroimaging applications that are discussed in this paper, are distinctive. Generally, the results of diagnostic neuroimaging are the most sensitive in terms of privacy, whereas those of brain-based lie and memory detection are likely to contain the least sensitive information.

However, irrespective of these differences in privacy sensitivity, these neuroimaging applications will yield a limited amount of personal data compared with (forensic) DNA testing. Cellular material, which is being obtained in the context of a DNA examination, contains much more sensitive personal information about the individual, eg regarding his health, ethnic origin, and familial connections. Although only a specific part of this information is relevant for the actual examination, taking cellular material implies that all sensitive information it contains will be acquired, just like a trawl catches marketable as well as undesirable fish. The four neuroimaging applications discussed above, however, do not serve as a trawl. The meaning, sensitivity and information richness of the data, which can be acquired through these applications, are, in prin-

90 *Cf.* Meynen *supra* note 15, at 2; Judy Illes et al., *Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging*, 50 B&C, 358 (2002).

91 *Cf.* Lisa Claydon, *Brain-Based Mind Reading for Lawyers: Reflecting on Possibilities and Perils*, 4 J. Law Biosci. 594, 598 (2017).

ciple, limited by the specific purpose for which a particular test is applied and the question that precedes the test. Depending on the aim of a particular neuroimaging application in a specific case, these applications yield information regarding a specific mental or neurological disorder, a risk of particular criminal behavior, the recognition of a specific stimulus, or the truthfulness of a specific answer to a particular question.

Note, however, that further scientific developments could change this view. If neuroimaging (together with machine-learning) was able to detect all current thoughts of the subject, in the manner of real-time neurotechnological mind reading,[92] it could be possible that the subject's thoughts, which are detected unfiltered, could also contain sensitive and highly personal information: regarding political opinions, sexual orientation, or religious beliefs.[93] Contrary to the four neuroimaging applications discussed above, the information that such types of real-time mind reading yield is not limited by the specific purpose of the test or the questions of the examiner, but depends on the specific items the subject (accidently) thinks about during the examination (such as his political or sexual preferences).

Returning to the requirement that an interference with the right to respect for private life must, to be justified, be proportionate with the legitimate aim(s) pursued. Just like coercive forensic neuroimaging, compulsory DNA testing aims to contribute to the detection and/or prevention of crime and the protection of the rights and freedoms of others.[94] According to the Grand Chamber, a strong consensus exists among the member States about compulsory DNA testing, and as a result, a narrow margin of appreciation is permitted to the States in the assessment of the permissible limits in this context.[95] In individual cases, the ECtHR has ruled that compulsory taking, examining, and retaining (cellular material and) DNA was—within the narrowed margin of appreciation—proportionate with the legitimate aims pursued.[96]

Contrary to compulsory DNA testing, as yet, no consensus exists about how to regulate coercive neuroimaging in criminal law. Moreover, the coercive use of neuroimaging raises ethical and moral issues, which on the one hand advocate a wider margin of appreciation in comparison with forensic DNA testing. However, on the other hand, being a pioneer in introducing new neuroimaging applications in the context of criminal law also requires the State to bear special responsibility in striking the right, proportionate balance between the competing interests. So, in the end, the

92 *Supra* note 16.

93 *Cf*. Gerben Meynen, *Ethical Issues to Consider Before Introducing Neurotechnological Thought Apprehension in Psychiatry,* 10 AJOB Neurosci. 8 (2019).

94 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 100 (December 4, 2008); ECtHR Peruzzo and Martens v. Germany, appl.nos. 7841/08, 57900/12, § 40 (June 4, 2013); ECtHR W. v. The Netherlands, appl.no. 20689/08, § 8 (January 20, 2009); ECtHR Van der Velden v. The Netherlands, appl.no. 29514/05, § 9 (December 7, 2006).

95 ECtHR (GC) S. & Marper v. UK, appl.nos. 30562/04, 30566/04, § 112 (December 4, 2008).

96 E.g. ECtHR Caruana v. Malta, appl.no. 41079/16, § 28–42 (May 15, 2018); ECtHR Peruzzo and Martens v. Germany, appl.nos. 7841/08, 57900/12, § 44–49 (June 4, 2013); ECtHR W. v. The Netherlands, appl.no. 20689/08, § 9 (January 20, 2009); ECtHR Van der Velden v. The Netherlands, appl.no. 29514/05, § 9 (December 7, 2006). In the Case of S. & Marper v. UK, however, the unlimited and indiscriminate retention of DNA and fingerprints of arrested individuals who were later acquitted or had the charges against them dropped, constituted a violation of article 8 ECHR.

margin of appreciation regarding compulsory DNA testing and coercive neuroimaging may be (more or less) the same. Furthermore, as I argued, the seriousness of the interferences made by current forms of coercive forensic neuroimaging regarding the right to respect for bodily integrity and personal data, will, in general, be similar to or less serious than the interferences made by compulsory DNA testing. So, if compulsory DNA testing is proportionate with the interests of detecting and preventing crime, it is likely that coercive forensic neuroimaging, generally constituting similar or less serious interferences with the right to respect for private life, could—within a comparable margin of appreciation—also be necessary in a democratic society in order to detect and prevent (serious) criminal offenses and to protect the rights and freedoms of others.

CONCLUSION

Coercive neuroimaging in criminal law interferes with the right to respect for private life in two ways: through an interference with the subject's (i) right to respect for bodily integrity and (ii) personal data. I have argued that the interferences made by coercive neuroimaging are generally similar to, or, less serious than, those of compulsory DNA testing. Unlike forensic DNA testing, as yet no legal, ethical and moral consensus exists as to how to regulate coercive neuroimaging in criminal law, which advocates the application of a wider margin of appreciation by the ECtHR. Alternatively, it could be argued that being a pioneer in introducing new neuroimaging applications in criminal justice narrows the margin of appreciation. Therefore, in the end, the margin of appreciation regarding compulsory DNA testing and coercive neuroimaging may be, more or less, the same. The ECtHR has repeatedly considered compulsory DNA testing to be proportionate with the aims of the prevention and detection of crime.[97] Taking into account a similar margin of appreciation and a similar seriousness of the interference with the right to respect for private life, I argued that it is likely that the coercive use of existing neuroimaging applications in criminal law could, under certain restricting legal conditions, be justified in light of the right to respect for private live, just like compulsory DNA testing.

DISCUSSION

In this paper, I have argued that coercive neuroimaging in criminal law interferes with the right to respect for private life contained in Article 8 ECHR, but it is likely that the interferences made can be justified. Therefore, in my view, the generic European human right to privacy arguably does not offer very strong protection to defendants or prisoners who are coercively subjected to brain-based lie or memory detection, diagnostic neuroimaging, or neuroprediction. This conclusion raises the interesting question of whether an additional, specific European human right should be developed in order to adequately protect the notion of 'mental privacy' in times of technological advances.[98]

On the one hand, the conclusions of this paper suggest that such a right is desirable. This is because the current general right to privacy, in all likelihood, does not offer very

97 But it has come down against the unlimited and indiscriminate retention of DNA in some circumstances.

98 *Cf.* Ienca & Andorno, *supra* note 7; Lavazza, *supra* note 71; Bublitz *supra* note 7.

strong protection to the privacy interests of defendants or prisoners whose brains are being examined against their will. On the other hand, however, the fact that under the generic European human right to privacy, some coercive neuroimaging applications seem to be permitted, could also indicate that the privacy interests regarding those applications may be less substantial than one would intuitively assume. This raises the question why we should develop a specific human right for the protection of brain data, but, for instance, not for the protection of DNA and other highly sensitive genetic information, which, just like brain data, already fall within the scope of the generic right to privacy contained within Article 8 ECHR.[99]

Furthermore, as the right to respect for private life may not offer strong protection against forensic coercive brain imaging, other European human rights, such as the privilege against self-incrimination (Article 6 ECHR) and the prohibition of ill-treatment (Article 3 ECHR), may be more promising with regard to particular forms of coercive neuroimaging.[100] In addition, the right to freedom of thought, conscience, and religion (Article 9 ECHR) could come into play,[101] since this right (also) prohibits coercion to express thoughts or to divulge a religion or nonreligion conviction.[102]

Before we start thinking about an additional human right to mental privacy, the overall protection that the current legal framework of European human rights offers with respect to coercive neuroimaging should be examined with precision. The need for a novel European human right to mental privacy, which should protect against coercively acquiring information from people's brains, deserves further discussion from both legal and ethical perspectives.

99 See e.g. Council of Europe/European Court of Human Rights, Bioethics and the case-law of the Court (2016).

100 *Cf.* Ligthart *supra* note 10.

101 Jan Christoph Bublitz, *Freedom of Thought in the Age of Neuroscienc,* 100 ARSP. 1, 25.

102 Ben Vermeulen & Marjolein van Roosmalen, *Freedom of Thought, Conscience and Religion*, in Theory and Practice of the European Convention on Human Rights 738–39 (Pieter van Dijk et al. eds. 2018); Harris et al., *supra* note 39, at 595.