How the brain deals with novelty and ambiguity: implications for neuroaesthetics

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Abstract Much of human cognition is "agent-centered," subjective, and in that sense relative, directed at resolving ambiguity and deciding, "What is best for me". This is very different from "veridical" cognition, directed at finding an objectively correct solution inherent in the task and independent of the agent. Understanding how the brain deals with ambiguity is central to the understanding of brain mechanisms of aesthetic judgment. It is equally important to understand how the brain deals with novelty, since in order to be aesthetically appealing the object of art must possess at least some degree of novelty and ambiguity. The frontal lobes in particular are central to agent-centered decision making and to dealing with novelty. Yet very little is available in the arsenal of cognitive paradigms used in the cognitive neuroscience research and in clinical neuropsychology test design to examine "agent-centered" decision making. The dearth of "agent-centered" cognitive paradigms severely limits our ability to understand fully the function and dysfunction of the frontal lobes. The cognitive bias task (CBT) is an agent-centered paradigm designed to fill this gap. CBT has been used as a cognitive activation task in fMRI, SPECT, and EEG, as well as in studies of normal development, addiction, dementia, focal lesions, and schizophrenia. This resulted in a range of findings, which had eluded more traditional "veridical" paradigms, and are reviewed here.

Keywords Neuroaesthetics · Agent-centered decision making · Prefrontal cortex · Cognitive bias task

1 Introduction

How does the brain deal with the novel, how does it deal with the familiar, and what does this have to do with neuroaesthetics? Attempts to uncover the criteria that guide our perception of the arts have been at the core of neuroaesthetics. What compels us to judge certain objects as beautiful and others as ugly? Unsurprisingly, most efforts to understand the cognitive and possibly even the neurobiological bases of aesthetic attitudes have centered on perception. Such efforts have revolved around the "golden ratio," which reflects certain relations between the elements of a visual form. It is essentially a perceptual criterion linked to the visual domain.

Yet other factors may play a role in our aesthetic judgment, and some of them may be universal, not limited to any single perceptual domain but pervading all of them. One such candidate criterion may reflect the ratio of the novel to the familiar in a piece of art—a "novelty/familiarity golden ratio." We do not know what it is, we do not even know whether it exists as a quantifiable value, but the possibility is tantalizing and worthy of further exploration.

It is intuitively self-evident that in order to be attractive, an object of art (visual, auditory, kinetic or otherwise) must be interesting, it must trigger our attention and curiosity.

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A boring object is not likely to be recognized as great art; hence a common tendency to break perfect symmetry in various artistic objects and striving toward artistic experimentation and innovation. On the other hand, we often judge art objects totally divorced from the familiar artistic idiom as repulsive. It is not uncommon for musical compositions or paintings recognized as great by later generations to be rejected and dismissed by the contemporaries. In totalitarian societies, this intolerance of radical artistic innovation may take rather ugly forms, like the campaign against "degenerate art" in Nazi Germany, or Nikita Khrushchev's infamous rant against contemporary art in Russia.

It appears that in order to be "attractive" an object of art must be novel but not too novel. Does this mean that an inviolate "novelty/familiarity" ratio exists, that it can actually be calculated, and then used to inform the artistic process?

The same question can be asked with respect to ambiguity. A true object of art allows multiple interpretations; it evokes different feelings and thoughts in different people. Yet it should possess some structure, however subtle and veiled. A completely amorphous object is not likely to be judged as aesthetically appealing. Is it possible to identify and quantify the degree of ambiguity that makes an object of art aesthetically appealing?

This may sound like a very ambitious agenda, and it may or may not prove realistic. Nevertheless, this clearly brings the very question of novelty versus familiarity and the question of ambiguity versus certainty into the domain of aesthetics, and the question about the neural mechanisms of processing the novel versus the familiar and the ambiguous versus certain into the domain of neuroaesthetics. In this paper, we will explore the brain mechanisms of processing cognitive novelty and cognitive familiarity, in the hope that this inquiry will eventually prove of relevance to neuroaesthetics, however indirect the path may be.

Two aspects of cortical organization are particularly relevant to the distinctions between cognitive novelty and familiarity, between ambiguity and certainty; and thus are of particular potential relevance to neuroaesthetics. The first one is the difference between the functions of the two cerebral hemispheres, whereby the right hemisphere appears to be particularly well suited for facing cognitive novelty and the left hemisphere for processing information in terms of well-established cognitive routines. The second one is the unique role of the frontal lobes in dealing with cognitive ambiguity. The review that follows aims to develop these themes in more detail.

2 Neuroanatomical substrates

Over the years, a wide ranging and diverse body of neuroanatomical literature has accumulated demonstrating structural and biochemical differences between the two hemispheres. These differences can be found both at the macro- and micro-anatomical levels, and in the neurotransmitter systems. In this section, we discuss how these differences between the two cerebral hemispheres may lead to functional differences, resulting in the right hemisphere's affinity for cognitive novelty and in the left hemisphere's affinity for established cognitive routines.

There is ample evidence of structural hemispheric difference across mammalian and primate species. Macroscopically, one example is the Yakovlevian torque where the hemispheres are "twisted" in a somewhat counterclockwise rotation (assuming a horizontal orientation) yielding an extension of the right frontal pole and left occipital poles with each of those being wider than their counterpart regions in the opposite hemispheres and a somewhat elongated and less angled lateral sulcus in the left hemisphere (see Toga and Thompson 2003; Bear et al. 1986; Lemay 1976; Weinberger et al. 1982). Others include larger left frontal operculum (Galaburda et al. 1978) and planum temporale (Dos Santos Sequeira et al. 2006; Sommer et al. 2008) in males. Microscopically, there appears to be a greater concentration of von Economo (spindle) neurons in the right hemisphere (Allman et al. 2010), and more orderly organization of longer myelinated pathways in the right hemisphere (Klingberg et al. 1999). Neurochemically, the catecholamines norepinephrine and dopamine are lateralized anatomically with distinct and complimentary involvement in behavior. There is evidence of higher concentrations of dopamine in the left hemisphere and norepinephrine in the right hemisphere in rats (Denenberg 1981; Glick et al. 1979, 1982; Oke et al. 1978, 1980; Pearlson and Robinson 1981; Robinson 1979; Slopsema et al. 1982) and humans with highest concentrations in the prefrontal cortex (Glick et al. 1982; Oke et al. 1978). Norepinephrine, with its preponderance in the right hemisphere, mediates exploratory behavior and orienting responses toward perceptual novelty in rats (Aston-Jones 1985; Aston-Jones and Bloom 1981; Delini-Stula et al. 1984; Foote and Bloom 1979; Kempf et al. 1974; Martin-Iverson et al. 1982; Watabe et al. 1982). This implies that norepinephrine, and concomitantly the right hemisphere, is critical in processing not only novel information but also external environmental stimuli. Dopamine, with its preponderance in the left frontal regions, mediates motor stereotypic behaviors among rats (Cools 1980; Iversen 1977; Lyons and Robbins 1975).

Such structural differences between hemispheres are assumed to result in functional differences for the organism. Curiously, models of hemispheric specialization in humans have primarily emphasized the evolutionarily discontinuous difference of verbal versus non-verbal specialization (Sperry 1966) despite evidence in non-human

mammalian species of structural hemispheric differences. Therefore, to be continuous with other mammalian species, the distinction between language and non-verbal functions must be merely a special case of a more fundamental distinction between the two hemispheres. Goldberg and Costa (1981) proposed that the right hemisphere is critical for processing novel cognitive situations, to which the pre-existing cognitive representations in the individual's cognitive repertoire are not readily applicable. By contrast, the left hemisphere is critical for processing with reliance on pre-existing, well-routinized cognitive representations and strategies, according to this model.

The novelty-routinization theory of hemispheric specialization (Goldberg and Costa 1981) is supported by more recent functional neuroimaging studies. These studies demonstrate a shift from right hemisphere activation on unfamiliar tasks to left hemisphere activation as the tasks move from unfamiliar to familiar, on time scales ranging from minutes to hours and from days to years. Martin et al. (1997) demonstrated a relative right-to-left hippocampal shift on PET for memorization tasks involving words, paralogs, drawings, and nonsense drawings within a single experiment. Shadmher and Holcomb (1997) demonstrated similar right-to-left shifts for within-experimental learning of a complex motor task. Henson et al. (2000) found evidence of right-to-left cortical activation in processing faces and symbols. Gold et al. (1996) demonstrated right-to-left shift in prefrontal cortex activation on working memory tasks as the task increased in familiarity. Examples of right-to-left shifts over longer time periods have been demonstrated among processing of familiar versus unfamiliar faces (Geffen et al. 1973; Marzi and Berlucchi 1977; Marzi et al. 1974; Rizzolatti et al. 1971; Umilta et al. 1985), familiarity with Morse code (Papcun et al. 1974), and trained musicians versus amateurs (Bever and Chiarello 1974; Gates and Bradshaw 1977; Johnson 1977; Wertheim and Botez 1961). It is notable that these shifts appear to occur for both verbal (Hellige 1976; Holtzman 1978; Miller and Butler 1980) and non-verbal stimuli (Gordon and Camron 1976; Holtzman 1978; Kittler et al. 1989; Reynolds and Jevves 1978; Ross and Turkewitz 1982; Ross-Kossak and Turkewitz 1984). Finally, electrophysiological evidence for the model was demonstrated by Kamiya et al. (2002), in finding higher frequency of gamma markers over the right hemisphere when a cognitive task is novel, with a shift to higher left gamma frequency as the task became familiar.

3 Agent-centered versus veridical cognition

Recent developments in neuropsychology and cognitive neuroscience have been characterized by a growing interest in decision making. The former has focused on tasks designed to measure deficits in these areas and the neuro-anatomical areas subsuming those processes (prefrontal cortices—see Lezak et al. 2004). The latter has focused on the process itself. However, neither has ever tried to understand it from the perspective of the individual in daily decision making. In other words, how are decisions made that will benefit the individual or gets the outcome the individual is seeking? To truly elucidate how one chooses something as being subjectively pleasing (or displeasing), one must understand how one makes decisions based upon individual preferences. We introduce a dichotomy, which is especially critical for capturing this distinct concept. It is the distinction between "veridical" and "agent-centered" cognition. This distinction is often ignored, or at least underemphasized in cognitive neuroscience, yet it is central to understanding the nature of decision making. We conceptualize a distinction between decision making and problem solving. Decision making is inherent to the individual and determined based upon individual preferences, biases, or experience without a clear cut right or wrong answer (i.e., actor-centered). In contrast, problem solving is deterministic where there is a clear-cut correct or incorrect choice that is not influenced by personal preference or bias (i.e., veridical).

Decision making presupposes the freedom to choose, and any consideration of such freedom must eventually address the issue of its brain mechanisms. Furthermore, the examination of free choice mechanisms will benefit from employing cognitive paradigms that require choice-making in underdetermined, ambiguous environments, in which distinct rational agents may differ in their choices. Appreciation of the importance of such decision making is reflected in the philosophical literature on imprecise probability and decision under uncertainty (ambiguity) (Halpern 2003; Keynes 1921; Kyburg 1974; Levi 1974). Yet (due to tradition rather than a well-reasoned research strategy), the paradigms typically deployed in cognitive neuroscience are notoriously ill-suited to address this issue. Research has traditionally relied on fully deterministic paradigms, whereby a subject is faced with a cognitive task characterized by a single correct response inherent in the task and independent of the agent, all other responses being incorrect. Even in the cutting-edge applications of cognitive neuroscience aiming to model complex decision-making in environments characterized by a high degree of uncertainty (e.g. neuroeconomics and social neuroscience), the cognitive paradigms used have attached to them an "objective" metric ranking certain response selections/decisions as being intrinsically "better" than others. Free choice can be exercised in fully deterministic situations, which is reflected in the fact that rational agents often make bad decisions. A cognitive paradigm would be helpful,

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which would permit a relatively unconstrained selection among a range of choices devoid of a priori, intrinsic "quality of choice" ranking in order to fully examine the brain mechanism of free will.

In order to fully examine the brain mechanisms of "free will," a cognitive paradigm would be helpful, which would permit a relatively unconstrained selection among a range of choices devoid of a priori, intrinsic "quality of choice" ranking. Such a paradigm would aim to examine decision making based on subjective preference, rather than directed at uncovering the intrinsically "correct" solution. We call such decision making, to which a "correct-incorrect" metric does not apply, "agent-centered" (as distinct from "veridical"). Using such tasks in conjunction with functional neuroimaging, neurostimulation, and other state-of-the-art techniques one may attempt to identify the brain networks critically involved in choice selection within such under constrained, and thus much more realistic, situations.

Real-life cognition is dominated by "agent-centered" decision making, which ranges from trivial (choosing from a restaurant menu) to life-shaping (career decisions). In either case, the "true–false" metric does not apply, since asserting that duck is an intrinsically correct choice and steak is an intrinsically false choice is an oxymoron, as is the assertion that medical school is an intrinsically correct choice and school of engineering is an intrinsically false choice. By contrast, "veridical" cognition is directed at solving problems characterized by intrinsically "true" and intrinsically "false" choices that do not depend on the agent. Here, too, the tasks may range from trivial $(5 + 5 = ?)$ to complex (what day of the week will be September 15, 4937?).

One can argue that in real life the cardinal decisions are agent-centered, while veridical cognition serves a supportive role, yet the arsenal of cognitive paradigms, used both in neuroscience research and as the basis for neuropsychological test design, is notoriously devoid of appropriate tools to study "agent-centered" cognition. The traditional focus on veridical cognition results in a highly contrived, artificial situation, whereby the research and clinical tools deployed to understand normal and abnormal cognition ignore some of the most fundamental aspects thereof.

This lamentable circumstance particularly compromises and impoverishes our ability to understand the contribution of the prefrontal cortex to complex cognition, since the prefrontal cortex and related structures are particularly central to "agent-centered" cognition (Goldberg 2009). This explains why many purported measures of executive control have notoriously poor ecological validity (Sbordone 2010) and why patients with prefrontal systems dysfunction can still do well on neuropsychological tests purported to assess prefrontal functions, yet are incapable

of navigating through life (see Goldberg 2009; Eslinger and Damasio 1985). Whereas, in cognitive neuroscience research various innovative paradigms proliferate departing to various degrees from the traditional "veridical" principle in paradigm design, very little of these developments percolated into clinical neuropsychology. Even the paradigms most commonly embraced in clinical neuropsychology as the "gold standard" of the functional assessment of the frontal lobes, e.g. Wisconsin Card Sorting Test; Stroop Test, etc., (see Lezak et al. 2004) are veridical in nature.

In order to correct this situation, a new generation of cognitive paradigms must be created, devoid of the "true–false" metric and based on subjective preference instead. In this paper, we will describe such a procedure, The Cognitive Bias Test (CBT), and will review its applications to several clinical and non-clinical populations. CBT is viewed as a prototype for a whole generation of future, yet to be designed, non-veridical agent-centered paradigms.

4 Cognitive bias task (CBT)

The cognitive bias task (CBT) is a novel, "agent-centered" paradigm that examines preferences made in a cognitive task devoid of intrinsically correct or intrinsically false choice (Goldberg et al. 1994a, b; Goldberg and Podell 1999). At the same time, CBT is sufficiently constrained to allow the experimenter a window into the underlying mental processes. CBT is intentionally simple, free of the complex plot layers, which often characterize the paradigms used in cognitive neuroscience research today in an attempt to emulate "real life" but at the cost of obfuscating any possible interpretation of findings. As a result, we have an experimental cognitive paradigm allowing us to examine "free will"—or at least "free choice"—in a rudimentary but uncluttered form.

CBT is designed to quantify the impact of cognitive context on response selection. It examines the subjects' response selection biases, ranging at its extremes from highly context-independent and inflexible (perseverative) to highly context-dependent (field-dependent). These two extreme selection biases are expressed as extremely low or high CBT scores, respectively. The task consists of 60 trials. Each trial involves a presentation of a simple geometric form ("target") and a subsequent presentation of two more geometric forms ("choices") vertically aligned just below the target (Fig. 1).

The instruction is to look at the target and then to choose the one choice that the subject *likes the best*. It is made clear that this is a true preference task and no choice is "better" than the other. The geometric forms are characterized along five binary dimensions (shape, color, size,
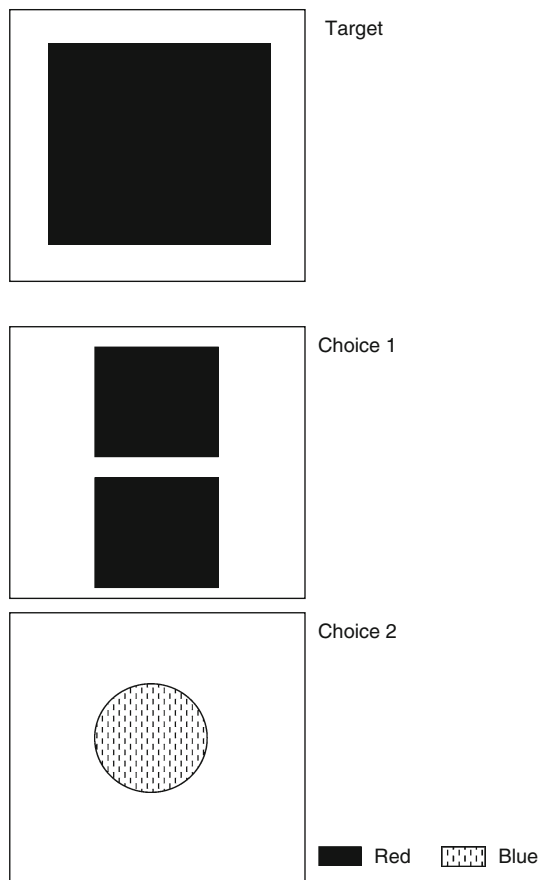
Fig. 1 Sample trial from the cognitive bias task (CBT). In this example, *choice #1* would yield a score of four as it matches the target stimuli along three of the five binary dimensions (*color*, *shape*, *filled*). *Choice #2* yields a score of zero, as it does not match the target on any of the five dimensions

filled/outlined, and one/two items in the frame); thus permitting 32 different items meticulously counter-balanced in the design across 60 trials. A number of constraints are built into the task, which are not apparent to the subject, thus implicitly limiting the number of choice options despite the subject's impression of "free choice." One such constraint is that on any given trial, one of the choices is perceptually more similar to the target than the other. This feature of CBT permits the design of two contrast, veridical tasks, which are physically identical to CBT in every respect except for the instruction: instead of asking the subject to make choices on the basis of subjective preference, the subjects are asked to choose on the basis of perceptual similarity to the target; or on the basis of perceptual dissimilarity from the target (for a detailed task description see Goldberg et al. 1994a). The availability of two disambiguated veridical analogs is an important feature of CBT design for two reasons. First, the "match for similarity" and "match for dissimilarity" task modifications become natural "subtraction" tasks whenever CBT is used as a cognitive activation task in functional

neuroimaging experiments (more on the subject later in the paper). Second, intact performance on the two "control" tasks serves as a check to ensure that the subject's individual preference on the "like the best" condition represents a true personal bias rather than an inability or cognitive deficit.

Since our design of CBT a number of years ago, it has been used to study normal adult cognition (Goldberg et al. 1994a; Stratta et al. 2000), cognitive development in children (Aihara et al. 2003), aging (Goldberg et al. 1997), cognitive characteristics of addiction (Verdejo-Garcia et al. 2006), cognitive changes in schizophrenia (Stratta et al. 1999), and (most relevant to this project) cognitive changes following lateralized frontal lesions (Goldberg et al. 1994a; Podell et al. 1995; Aoyagi et al. 2005). CBT has also been successfully used as an activation task in fMRI and SPECT studies (Vogeley et al. 2003; Shimoyama et al. 2004). We will describe some of these studies in greater detail below.

4.1 Sex differences in normal subjects

Gender differences in normal cognition have been well elucidated over the past several decades and were the focus of neuropsychology in the sixties and seventies (Springer and Deutsch 2001). Unsurprisingly, it focused overwhelmingly on the differences in veridical cognition, often leading to potentially inflammatory (and not always replicated) claims ascribing performance "superiority" on certain cognitive tasks to one gender over the other. The most common among such claims is the controversial and far from clearly replicable accretion of female "superiority" in verbal cognition and male "superiority" in spatial cognition (see Springer and Deutsch 2001). Overall, the effect size for such studies is typically on the magnitude of a 0.25 SD; enough to find differences at the group level, but with a large amount of overlap at the individual level. We feel that the restriction to use veridical-based cognitive tasks has limited or obscured the true gender difference and with the proper paradigm (i.e., actor-centered tasks) one would have a clearer understanding of gender differences in cognition.

By contrast, CBT allows one to focus on gender differences in cognitive styles rather than in cognitive abilities. Normal, neurologically healthy subjects exhibit a wide range of individual differences in selection preferences on CBT (Goldberg et al. 1994a; Stratta et al. 2000). Furthermore, they exhibit significant group differences, e.g. gender differences among healthy, neurologically intact subjects in the ways "free choice" is exercised (Fig. 2). Right-handed males make their choices in a relatively context-dependent fashion (i.e. their choices are strongly influenced by the changing perceptual context). By contrast, right-handed females are relatively context-independent (i.e. their

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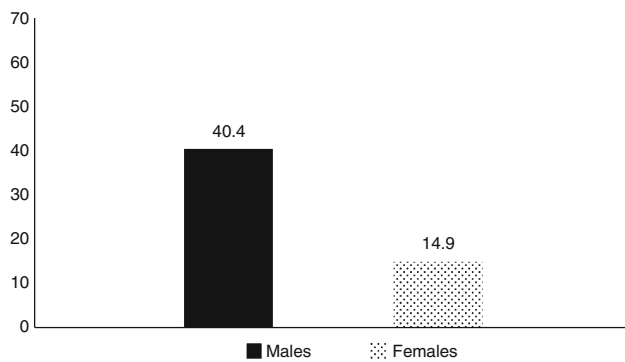
Fig. 2 CBT Score by gender. A higher CBT score reflects a greater degree of context-dependent response style. A lower CBT score reflects a greater degree of context-independent response style. A minimum score of zero represents complete context-independent scoring (here, the subject chose the most similar and different response choice 50 % of the time, each). A maximum score of 70 indicates that the subject chose the most similar response choice on every trial)

Fig. 3 CBT score by gender and handedness in healthy subjects

choices are guided by stable perceptual preferences unrelated to the changing perceptual context). Given the non-veridical nature of CBT, these differences in response selection profiles have nothing to do with the quality of performance, but rather capture different response selection styles in ambiguous environments. When given specific directions on how to complete the task (thus turning it into a veridical-based task) both male and female groups perform identically and the previous gender difference on CBT is removed.

Obviously, one should be careful not to over-generalize based upon a single experimental paradigm and a limited subject sample. Our sample consisted of adult individuals. Therefore, we do not know whether the differences reported by us are innate or whether they arise at certain developmental stages, e.g. with puberty. However, Aoyagi et al. (2005) demonstrated a step-wise developmental pattern in CBT scores (advancing to a more context-dependent response pattern) in right-handed males consistent with known cognitive developmental stages. Nor do we know if these sex differences in cognitive styles persist into the advanced age. Additional studies will have to be conducted to address these issues and the findings may have interesting ramifications for the optimal didactic methods selection for females versus males at various educational levels, for job selection counseling and vocational training, etc.

4.2 Handedness differences in normal subjects

The relationship between handedness and cognition has also been of interest for decades (see Springer and Deutsch 2001). We demonstrated considerable interaction between gender, handedness, and CBT performance patterns
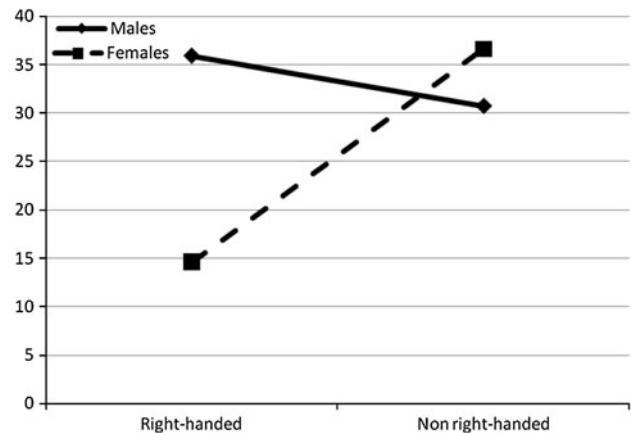
(Goldberg et al. 1994a; Fig. 3). This finding is particularly intriguing, since earlier attempts to demonstrate consistently a relationship between handedness and cognitive variables resulted in failures. It thus appears that the agent-centered paradigm instantiated in the CBT is capable of characterizing cognition in ways, which eluded the more traditional veridical paradigms.

4.3 Functional neuroimaging studies using CBT in healthy subjects

It is tempting to assume theoretically that agent-centered decision making relies particularly on the prefrontal cortex. But how valid is this assumption? The empirical test of this assumption is best conducted using CBT as a cognitive activation task in various functional neuroimaging modalities. (As mentioned earlier, CBT is particularly well suited for use in functional imaging research, since it comes with natural "subtraction" tasks. It is common in functional neuroimaging research to administer the critical task in conjunction with a baseline task or tasks used for comparison. CBT has been designed in such a way that on every trial one choice is more similar to the target than the other. This permits two "subtraction" tasks that retain all the physical characteristics of CBT but are no longer preference "agent-centered" tasks: (a) match for similarity; (b) match for difference).

Patterns of regional cortical activation associated with CBT have been studied with several neuroimaging modalities. Vogeley et al. (2003) used CBT as a cognitive activation task in functional magnetic resonance imaging (fMRI). Shimoyama et al. (2004) used CBT as a cognitive activation task in high resolution single photon emission computerized tomography (SPECT). Kamiya et al. (2002) used electroencephalography (EEG) to map the regional scalp distribution of gamma frequency (30–40 Hz), while subjects performed a modified CBT version (gamma

frequency is commonly presumed to be an electrophysiological marker of mental effort). All three studies have demonstrated preferential activation of the prefrontal cortex when the task was one of subjective preference-based choice.

4.4 Cognitive characteristics of addiction

What distinguishes the cognitive profile of an addict from that of healthy individuals? What are the cognitive risk factors, the cognitive traits predisposing one to addiction? What are the cognitive consequences of long-term addiction? All these questions are of great public health importance and relevance, and they have triggered a large body of research. The assumption is often made that executive functions must be particularly compromised in addiction. This is a perfectly reasonable assumption, but we know that "executive functions" is a rather generic term that subsumes a number of loosely interrelated constructs, the unifying theme being that they all are somehow mediated by the frontal lobes. So exactly which executive functions are compromised in addiction?

Verdejo-Garcia et al. (2006) addressed this question in a sample of heroin addicts, whose performance on neuropsychological tests was compared to that of demographically matched healthy controls. The authors were particularly interested in the subjects' performance on CBT and on the Iowa Gambling Test (IGT), which while being essentially veridical (i.e. characterized by intrinsically "good" and "bad" choices), more closely mimics real-life decision making than most tests (Bechara et al. 2000) Indeed, the heroin addicts adopted suboptimal performance strategies on IGT. However, it was the difference in CBT performance between the heroin addicts and healthy controls that was a particularly striking outcome of the study. By contrast, there was no difference between the two groups on the disambiguated, veridical versions of CBT. So, it appears that agent-centered decision making is particularly impaired in addiction. The lack of association between IGT (veridical) and CBT (actor-centered) scores in addicts adds further support between the dissociation of veridical and actor-centered decision making.

4.5 Cognitive characteristics of Alzheimer's type dementia

Efforts to characterize the cognitive impairment of Alzheimer's type dementia (DAT) have traditionally focused on memory impairment. This emphasis is also reflected in the Diagnostic and Statistical Manual (DSM-IV) commonly used in the United States for the clinical diagnosis of mental health disorders. According to DSM-IV, the diagnosis of dementia requires the presence of memory impairment as an obligatory component, accompanied by an impairment of several other cognitive domains (The unfortunate consequence of this narrow formulation is, of course, that its mechanical application would disqualify Pick's disease and certain manifestations of Lewy body disease from dementia diagnosis—and absurdity on the face of it). This emphasis on memory impairment in dementias has indeed been a mixed blessing, since it diverted research from other cognitive domains in dementias. Today, it is increasingly recognized that the executive functions of the frontal lobes are also extremely vulnerable in dementias.

Goldberg et al. (1997) compared CBT performance in patients with very early, "mild" DAT, more advanced "moderate" DAT, and healthy age-matched controls. Changes in performance were evident already in mild DAT when compared with healthy controls. By contrast, changes in the veridical CBT version ("match to similarity") became apparent much later in the disease process, only in the more advanced "moderate" DAT group. This highlights the vulnerability of the prefrontal cortex at very early stages of Alzheimer's type dementia, which becomes apparent once sufficiently sensitive cognitive probes of frontal-lobe function are deployed.

4.6 Lateralization and sex differences of frontal lobe functions: lesion studies

Hemispheric specialization has historically been among the central themes of neuropsychology (Springer and Deutsch 2001), but the frontal lobes have been on the periphery of this inquiry. As long as the theoretical framework guiding research on hemispheric specialization was one of verbal versus visuo-spatial distinction, the focus has understandably been on the posterior cortical structures, with any functional lateralization in the prefrontal cortex considered only as an afterthought. To the extent that the functional lateralization in the prefrontal cortex was considered at all, it was usually as an extension of the verbal versus visuo-spatial dichotomy: the left prefrontal cortex as the medium of verbal generativity and the right prefrontal cortex as the medium of visuo-spatial generativity (see Lezak et al. 2004). Few have introduced new conceptual frameworks for understanding functional lateralization within the prefrontal cortex. The hemispheric encoding/retrieval asymmetry (HERA) model of Endel Tulving and associates (Nyberg et al. 1996; Habib et al. 2003) was one such model introduced within the past few years. This historic relative lack of interest in the functional lateralization in the prefrontal cortex flies in the face of a number of morphological, cytoarchitectonic, and biochemical findings that were noted above. As noted earlier in this discussion, Yakovlevian torque implies a wider right than left frontal pole (Toga and Thompson 2003; Bear et al. 1986; Lemay 1976;

Weinberger et al. 1982); von Economo cell (also known as the spindle cells) are more prolific in the right than left prefrontal cortex (Allman et al. 2010); dopamine pathways are more prolific in the left than right frontal regions (Denenberg 1981; Glick et al. 1979, 1982; Oke et al. 1978, 1980; Pearlson and Robinson 1981; Robinson 1979; Slopsema et al. 1982). Furthermore, some of these asymmetries are not limited to humans and are found across a wide range of mammalian species. To the extent that one believes in a relationship between structure/biochemistry and function—and most of us do, this leads to two logical conclusions (a) robust functional differences must exist between the left and right frontal lobes; and (b) at least some of these functional differences are irreducible to the verbal versus visuo-spatial dichotomy.

So why have these differences been overlooked in earlier research? The answer may be that the commonly used veridical paradigms are just not sensitive enough to, or perhaps are not altogether appropriate for eliciting, the functional lateralization in the prefrontal cortex (Podell et al. 1995).

Goldberg et al. (1994a) studied the effects of lateralized prefrontal lesions on CBT performance and found robust hemispheric and gender differences in right-handed patients with lateralized focal frontal lesions (Fig. 4)—probably the most robust such differences ever reported in the literature. The lesion effects in males are highly asymmetric: left prefrontal lesions produce extremely context-independent (perseverative) response selection, and right prefrontal lesions produce extremely context—independent (field-dependent) response selection relative to healthy controls. In females, the lesion effects are symmetric, both left and right prefrontal lesions producing extremely context-dependent response selection relative to normal controls. This sex difference in the degree of lateralization of frontal-lobe functions is broadly consistent with the neuroanatomical findings of a less articulated Yakovlevian torque in females than in males.
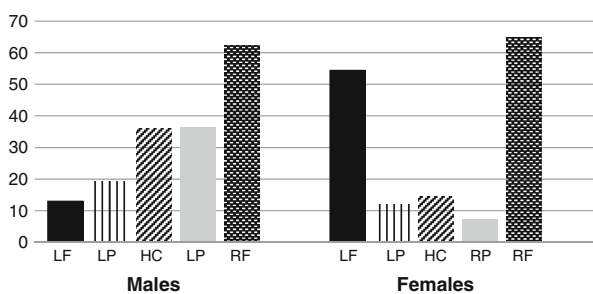
Fig. 4 CBT score in right-handed male and female with quadrant lesions. *LF* left frontal (male 5; female 5), *LP* left posterior (male 3; female 1), *HC* healthy control (male 21; female 14), *RP* right posterior (male 5; female 4), *RF* right frontal (male 8; female 4)

CBT appears to be more sensitive to direct frontal-lobe damage (as in stroke, trauma or neoplasms), and in more neuroanatomical specific ways, than any of the more commonly used cognitive paradigms. This becomes evident when CBT's ability to separate the effects of left versus right prefrontal lesions is compared to that of the Wisconsin Card Sorting Test (WCST), which has been traditionally considered the "gold standard" of assessing frontal-lobe function and dysfunction. CBT separates the effects of left versus right prefrontal lesions (Fig. 4), whereas WCST fails to do so (Fig. 5) (Podell et al. 1995).

Additional, intriguing findings were obtained in a (by necessity) small sample of naturally left-handed patients with lateralized lesions (Goldberg et al. 1994a). The effects of lesions in this cohort were distinctly different from, and in some way opposite to, those documented in the naturally right-handed patients (Fig. 6a, b). While this finding is clearly in need of replication due to very small left-handed sample size, if confirmed it may well be the first in the literature demonstration of a double-dissociation between handedness and performance on a cognitive variable.

Using CBT in patients with lateralized frontal lesions, it was possible to show that the left and right frontal systems play different, and in males synergistically opposite, roles in response selection in ambiguous environments. To the best of our knowledge, these studies were among the first to examine the neural basis of choice-making in underdetermined ambiguous "agent-centered" situations. Aside from their potential theoretical value, these findings are of great potential practical importance in the design of cognitive remediation procedures individualized according to lesion side (e.g. in the anterior cerebral artery strokes), sex, and handedness.
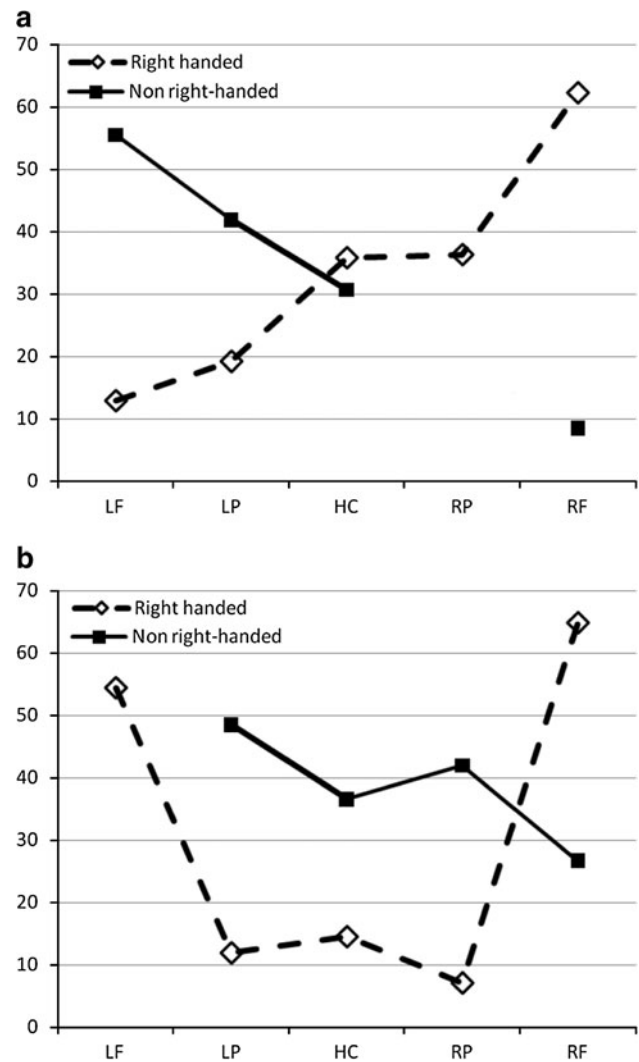
Inquiry into the role of the prefrontal cortex and its different subdivisions in mediating choice-making in under-constrained environments is of great potential relevance to diverse areas, ranging from clinical neuroscience to education to neuroeconomics. Prior research, including our own, has shown that the frontal lobes are central to most complex, "meta-cognitive" levels of our mental life and are particularly important in decision making involving novel situations characterized by a high degree of uncertainty. While extensive literature exists on the roles of the prefrontal cortex in meta-cognition and decision making, it is conspicuously remiss in one particular regard: differential contributions of the left versus right frontal lobes to these processes. As mentioned earlier, traditionally, the inquiry into functional differences between the two cerebral hemispheres has emphasized posterior temporo-parietal structures, while largely ignoring the prefrontal cortex. Yet gross morphological, cellular, and biochemical differences between the left and right prefrontal regions have been described, which are likely to translate into functional

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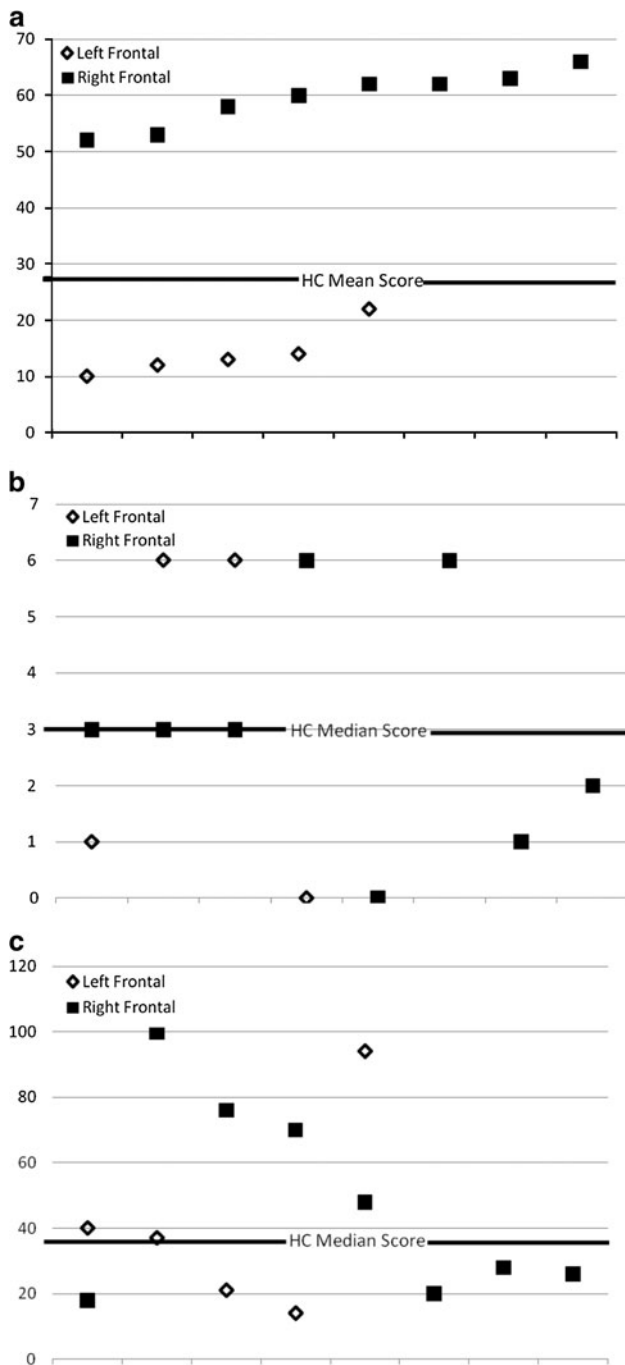
Fig. 5 **a** Individual CBT scores in male left and right frontal lesion subjects compared to healthy control (HC) mean score. **b** Wisconsin Card Sorting Test categories completed in male left and right frontal lesion subjects compared to healthy control (HC) median score. **c** Wisconsin Card Sorting Test perseverative responses in male left and right frontal lesion subjects compared to healthy control (HC) median score

Fig. 6 **a** CBT scores in right-handed and non-right handed males subjects with quadrant lesions. *LF* left frontal ($n = 2$), *LP* left posterior ($n = 3$), *HC* healthy control ($n = 19$), *RP* right posterior ($n = 0$), *RF* right frontal ($n = 2$). **b** CBT scores in right-handed and non-right handed female subjects with quadrant lesions. *LF* left frontal ($n = 0$), *LP* left posterior ($n = 2$), *HC* healthy control ($n = 19$), *RP* right posterior ($n = 2$), *RF* right frontal ($n = 3$)

4.7 Lateralization of frontal lobe functions: functional neuroimaging studies

Using brain pathology as a basis for inferring the principles of normal brain functions has proved extremely productive over the years. Nonetheless, this approach has all the pitfalls of being indirect. It is necessary to examine further the complementary hemispheric contributions to "free choice" in healthy individuals using the combination of state-of-the-art functional neuroimaging and brain stimulation with techniques such as transcranial magnetic stimulation (TMS). CBT is uniquely suited for use in such future studies, because it is extremely sensitivity to lateralized

differences. What are these functional differences and how do they manifest themselves in decision making? What is the optimal integration of the left and right prefrontal contribution to decision making? These are some of the questions to be addressed in the future research.

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lesion effects. Shimoyama et al. (2004) used a modified version of CBT (mCBT) as a cognitive activation task in SPECT in a sample of young adult males. Bilateral dorsolateral prefrontal activation was evident. Additionally, left inferior prefrontal activation was associated with a context-dependent response selection strategy. This is broadly consistent with the lesion studies discussed earlier.

4.8 Neurodevelopmental studies

Is the frontal-lobe functional lateralization pattern described in the previous sections fundamental, or is it an emergent consequence of something else, e.g. language acquisition? Aoyagi et al. (2005) addressed the issue by administering a modified version of CBT (mCBT) to a sample of children with left and right frontal focal lesions/epileptic foci, as well as to matched healthy controls. The effects of lateralized frontal lesions in children were similar to those documented in the adults. Thus, the authors concluded that the functional lateralization properties in the frontal lobes captured by CBT are "fundamental" and "biological" in nature.

Does this mean that the choice behavior in underconstrained, "agent-centered" situations remains unchanged with age? Not necessarily. Evidence exists that the two cerebral hemispheres mature at somewhat different rates, right earlier than left, and this may affect the way decisions are made at different neurodevelopmental stages. Aihara et al. (2003) studied response selection patterns on mCBT in different male age groups. Gradual shift was evident from predominantly context-independent choice selection (5–7 years old boys) to intermediate choice selection (7–9 years old boys) to predominantly context-dependent choice selection (13–16 years old boys). This is consistent with a change in the balance of the two prefrontal systems in decision making with age.

4.9 Lateralization of frontal-lobe dysfunction in schizophrenia

Schizophrenia is being increasingly viewed as a syndrome at the intersect of many possible causes, rather than as a cohesive disorder, which makes any neuroanatomical generalization about schizophrenia potentially spurious. Nonetheless, frontal-lobe dysfunction is a unifying theme and a particularly constant finding across a large body of research. In particular, left prefrontal dysfunction is frequently documented (Schobel et al. 2009; Wolf et al. 2008). Stratta et al. (1999) administered CBT to a sample of schizophrenic patients and documented a preponderance of context-independent reasoning in both female and male patients compared to healthy controls. This is consistent with the lesion studies described earlier in this paper,

linking extreme context-independent cognition to left prefrontal lesions.

5 Conclusions

Understanding the mechanisms of adaptive and maladaptive decision making has become one of the central themes of neuropsychology and cognitive neuroscience. Considerable strides have been made in the design of cognitive paradigms aimed at studying these processes in a more realistic context of (usually economic) gains or losses. Yet two broad domains of decision making remain largely ignored, despite their centrality to human cognition. One is the domain of agent-centered decision making, which is subjective preference based and to which no objective "good-bad" metric applies. The other one is the domain of cognitive novelty.

These two domains are of particular relevance to neuroaesthetics. As efforts are underway to develop innovative experimental paradigms to study the brain mechanisms of novelty and agent-centered decision making, cognitive neuroscience and neuropsychology will be in an increasingly strong position to contribute to neuroaesthetics. Far-fetched as it may sound today, it may yet be possible to formulate and quantitatively express the "novelty-familiarity" and "ambiguity-certainty" golden ratio defining great objects of art.

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