

# Challenges in accurately modeling the complexity of human ingestive behavior: the influence of portion size and energy density of food on fMRI food-cue reactivity<sup>1</sup>

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Ingestive behavior is determined by a complex interaction between neurophysiologic and behavioral and environmental contributors that begins early in life. A better understanding of this complex regulatory system is needed to account for the multifaceted nature of human ingestion. Among the influences on ingestion, increased portion size (PS)<sup>5</sup> has been associated with increased energy intake independent of the energy density (ED) of food in children and adults in controlled (i.e., laboratory) and free-living conditions (1). The hedonic effects of ED have been studied in both adult and child neuroimaging studies (2, 3). In this issue of the Journal, the report by English et al. (4) on neurophysiologic correlates of PS and ED in children represents a necessary step towards furthering our understanding of these complex phenomena.

English et al. (4) measured fMRI BOLD responses in healthy children (7–10 y old) during a presentation of food images representing large PS, small PS, high ED, and low ED in a blocked design and performed an exploratory whole-brain analysis to begin to shed light on brain involvement in processing of these visual cues. The authors explored the main effects of PS, ED, and their interaction with and without controlling for several covariates, including BMI *z* score, sex, fullness at baseline, and mean difference in liking of the stimuli within categories. Linear correlations between eating behavior questionnaires and high-ED compared with low-ED fMRI contrasts were also examined.

Categorizing food stimuli on the basis of high and low ED and PS addresses an often-ignored gap in the literature, because differences in food-cue reactivity of the brain in response to PS and ED may exist that are masked when more-general food and object contrasts are considered. For instance, large PS was associated with decreased BOLD responses in the inferior frontal gyrus (IFG; i.e., Brodmann area 47) compared with small PS. This contrast was driven mainly by the specific combination of large-PS, low-ED food stimuli. As the authors note, Brodmann area 47 (IFG) is often interpreted as being involved with cognitive or attentional control processes related to ingestion (5, 6). In this case, an additional interpretation could be that children simply dislike large-PS, low-ED foods and thus are not attending to them as strongly or for as much time. In subsequent analyses, the authors found that the effects of PS on the food-cue reactivity of the IFG appear to be influenced by liking of

images coupled with the appetitive state (i.e., self-reported fullness). Thus, by examining the nature of the response to different aspects of the food stimuli (PS, ED), the authors provide novel insight into the need to carefully consider stimulus properties and individual context (e.g., liking, hunger or fullness) when examining the neurological underpinnings of ingestion.

Paralleling previous literature on food-cue reactivity in adults, activation in a number of regions was associated with ED (7, 8). Of particular interest are the increased activations in the precentral gyrus in response to high-ED food. One plausible interpretation is an increased motor response to these images, possibly suggesting that high-ED foods may be associated with enhanced motor readiness to ingest (8). This is further supported by the negative association observed between slow eating and high-ED compared with low-ED contrast in the precentral gyrus in the current study.

Finally, the authors show a significant PS × ED interaction in the superior temporal gyrus, which was driven by decreased reactivity to large-PS, low-ED food and increased reactivity to small-PS, low-ED food. Although the functional significance of this interaction remains to be completely understood, the demonstration that PS and ED interact in fMRI food-cue reactivity paradigms provides novel insight to guide future fMRI studies.

Although English et al. provide a novel starting point for future inquiry with their approach to studying the complex ingestive process, considerable caution is urged in the interpretation and application of these findings on the basis of certain methodologic caveats. As noted by the authors, differences in visual qualities of the images (e.g., color, consistency, overall appearance) may have influenced the outcomes. This issue can be readily addressed in future studies by including control images that are matched on these dimensions (8).

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<sup>5</sup> Abbreviations used: ED, energy density; IFG, inferior frontal gyrus; PS, portion size.

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Another important methodologic consideration involves the appropriate control for type I error rate during image thresholding. The current study used a Monte Carlo–based cluster-extent correction that depends on the smoothness across voxels (spatial autocorrelation) to estimate a null distribution of cluster sizes. The logic of this correction is that greater smoothness will lead to larger clusters due to chance alone. Recent studies have suggested that key assumptions of such corrections (e.g., constant smoothness) are often violated, which can inflate error rates as high as 70% (9). Beyond possible assumption violations, English et al. also rely on an implausibly low spatial smoothness estimate. The reported 1-mm<sup>3</sup> estimate of smoothness in the residual data is implausible given the 8-mm smoothing of the functional images during preprocessing and the up-sampling of the images from 3 mm<sup>3</sup> to 1 mm<sup>3</sup>, which turns each original voxel into 27 voxels that share some information. The low smoothness estimate results in extremely small cluster sizes ( $k = 14$ ) being significant, making it difficult to rule out false positives for some of the reported effects. Future studies would benefit from the use of nonparametric resampling techniques for estimating the null distribution of cluster sizes that are not dependent on smoothness estimates and that require fewer assumptions (9).

Another area in need of reconsideration involves the use of post hoc tests on parameter estimates extracted from significant clusters identified in previous contrasts. The use of the same data for selection and post hoc testing results in inflated error rates due to nonindependence between the selection criteria and tests (10). Extracting parameter estimates from clusters that show a significant interaction can be useful for visualization purposes, but caution is advised when interpreting any effect sizes, error bars, and tests based on those estimates. Furthermore, because any effects are likely to be inflated in selected regions, post hoc control for additional variables (e.g., sex, BMI, hunger) is likely to be ineffective. Control variables must be included in the original group-level regression before voxel selection.

Despite these limitations, English et al. have taken a unique approach in an attempt to improve our understanding of how children process visual information related to specific characteristics of a typical real-world food encounter (combined PS and ED). Their attempts to delineate the neural basis of salient aspects of the ingestive experience (i.e., PS and ED), coupled with

a more translational ingestion paradigm, should serve as an impetus for future innovative research to understand this multifaceted and complex phenomenon. Their findings lend support to the notion that overly simplistic approaches may miss salient aspects of the food experience that influence neurophysiologic reactions to food stimuli.

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